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(57) Abstract <p>The invention provides human RNA-associated proteins (RNAAP) and polynucleotides which identify and encode RNAAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonist. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of RNAAP.</p>																																																			
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RNA-ASSOCIATED PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of RNA-associated proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, immune/inflammatory, and reproductive disorders.

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BACKGROUND OF THE INVENTION

Ribonucleic acid (RNA) is a linear single-stranded polymer of four ribonucleotides, ATP, CTP, UTP, and GTP. In most organisms, RNA is transcribed as a copy of deoxyribonucleic acid (DNA), the genetic material of the organism. RNA copies of the genetic material encode proteins or serve various structural, catalytic, or regulatory roles in organisms. RNA is classified according to its cellular localization and function. Messenger RNAs (mRNAs) encode polypeptides. Ribosomal RNAs (rRNAs) are structural RNAs that are assembled, along with ribosomal proteins, into ribosomes, which are cytoplasmic particles that function in the translation of mRNA into polypeptides. Transfer RNAs (tRNAs) are cytosolic adaptor molecules that function in mRNA translation by recognizing both an mRNA codon and the amino acid that matches that codon. Heterogeneous nuclear RNAs (hnRNAs) include mRNA precursors and other nuclear RNAs of various sizes. Small nuclear RNAs (snRNAs) are a part of the nuclear spliceosome complex that removes intervening, non-coding sequences (introns) and rejoins exons in pre-mRNAs.

RNA-binding proteins are essential for a wide variety of cellular and developmental functions. They participate in RNA processing, editing, transport, localization, stabilization, and the posttranscriptional control of mRNAs. They also provide the protein component of ribosomal RNA, transfer RNA, and other ribonuclear proteins. The RNA binding activity of these proteins is mediated by specific RNA-binding domains contained within the proteins. A variety of conserved RNA binding motifs have been defined through comparisons of amino acid homologies and structural similarities within these RNA-binding domains. These motifs include the RNP motif, an arginine-rich motif, the zinc-finger motif, the Y-box, the KH motif, and the double-stranded RNA-binding domain (dsRBD), all of which are characterized by specific consensus sequences (Burd, C. G. and Dreyfuss, G. (1994) Science 265:615 - 621).

RNA Processing

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Various proteins are necessary for processing of transcribed RNAs in the nucleus. Pre-mRNA processing steps include capping at the 5' end with methylguanosine, polyadenylating the 3' end, and splicing to remove introns. The spliceosomal complex is comprised of five small

nuclear ribonucleoprotein particles (snRNPs) designated U1, U2, U4, U5, and U6. Each snRNP contains a single species of snRNA and about ten proteins. The RNA components of some snRNPs recognize and base-pair with intron consensus sequences. The protein components mediate spliceosome assembly and the splicing reaction. Autoantibodies to snRNP proteins are found in the blood of patients with systemic lupus erythematosus (Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY, p. 863).

Heterogeneous nuclear ribonucleoproteins (hnRNPs) have roles in functions that include splicing, exporting of the mature RNAs to the cytoplasm, and mRNA translation (Biamonti, G. et al. (1998) Clin. Exp. Rheumatol. 16:317-326). Some examples of hnRNPs include the yeast proteins Hrp1p, involved in cleavage and polyadenylation at the 3' end of the RNA; Cbp80p, involved in capping the 5' end of the RNA; and Npl3p, a homolog of mammalian hnRNP A1, involved in export of mRNA from the nucleus (Shen, E.C. et al. (1998) Genes Dev. 12:679-691). A common feature of all of these RNA-binding proteins is a glycine-rich region in the form of RGG repeats. HnRNPs have been shown to be important targets of the autoimmune response in rheumatic diseases (Biamonti et al., supra).

An important means of regulating the function of hnRNPs is by methylation of arginine residues. The hnRNPs contain 65% of the methylated arginine residues in the cell nucleus. Methylation occurs within the RGG domain. Methylated arginine residues are also found in non-hnRNP RNA-binding proteins, all of which contain RGG repeats. The yeast enzyme, Hmt1p, is responsible for methylation of Npl3p and Hrp1p. In HMT1 null mutants, methylation of these proteins is not detectable, and poly(A⁺)RNA accumulates in the nucleus. A molecular model predicts that Cbp80, Npl3p, and Hrp1p form a complex with mRNA to package the RNA for export from the nucleus, and that methylation plays a role in the efficiency of this packaging. Formation of this export complex is crucial for efficient exit of mRNA out of the nucleus. (Shen, supra.) A human homolog of Hmt1p, HRMT1L2, has been identified and is required for methylation of arginine residues in the RGG repeats of hnRNP A1. (Scott, H.S. et al. (1998) Genomics 48:330-340.) Also, viral RNA-binding proteins, such as the herpes simplex virus ICP27 protein, are known to be arginine-methylated. This exploitation of the cellular export machinery may facilitate maturation of viral RNAs. (Shen, supra.)

Human myxoid liposarcomas have been shown to contain a chromosomal translocation [(t12;16)(q13;p11)] wherein the gene coding for an inhibitory, growth arrest-associated transcription factor, known as CHOP (C/EBP homologous protein), is fused to the gene for TLS (translocated in liposarcoma), a nuclear RNA-binding protein that contains an RNP motif. TLS has been shown to function as an RNA chaperone, shuttling RNA into and out of the nucleus

(Zinszner, H. et al. (1997) J. Cell Sci. 110:1741-1450). The fusion of TLS with CHOP serves to convert a transcription factor involved in growth arrest into one associated with abnormal cell proliferation (Crozat, A. et al. (1993) Nature 363:640-644). Subsequent work has shown that TLS and its homologs (e.g., EWS, associated with Ewing's sarcoma) comprise the N-terminal portion of a number of fusion oncoproteins associated with sarcomas as well as with certain human acute myeloid leukemias (AMLs), secondary AMLs associated with myelodysplastic syndrome, and certain chronic myeloid leukemias (Aman, P. et al. (1996) Genomics 37:1-8; Zinszner, H. et al. (1997) Oncogene 14:451-461; Pereira, D.S. et al. (1998) Proc. Natl. Acad. Sci. USA 95:8239-8244).

Many snRNP and hnRNP proteins are characterized by an RNA recognition motif (RRM) (Birney, E. et al. (1993) Nucleic Acids Res. 21:5803-5816). The RRM is about 80 amino acids in length and forms four β -strands and two α -helices arranged in an α/β sandwich. The RRM contains a core RNP-1 octapeptide motif along with surrounding conserved sequences. In addition to snRNP proteins, examples of RNA-binding proteins which contain the above motifs include heteronuclear ribonucleoproteins which stabilize nascent RNA and factors which regulate alternative splicing. Alternative splicing factors include developmentally regulated proteins, specific examples of which have been identified in lower eukaryotes such as Drosophila melanogaster and Caenorhabditis elegans. These proteins play key roles in developmental processes such as pattern formation and sex determination, respectively (Hodgkin, J. et al. (1994)

Development 120:3681-3689).

RNA Stability and Degradation

RNA helicases alter and regulate RNA conformation and secondary structure by using energy derived from ATP hydrolysis to destabilize and unwind RNA duplexes. The most well-characterized and ubiquitous family of RNA helicases is the "DEAD-box family," so named for the conserved B-type ATP-binding motif which is diagnostic of proteins in this family. Over 40 DEAD-box helicases have been identified in organisms as diverse as bacteria, insects, yeast, amphibians, mammals, and plants. DEAD-box helicases function in various processes such as translation initiation, splicing, ribosome assembly, and RNA editing, transport, and stability. Some DEAD-box helicases play tissue- and stage-specific roles in spermatogenesis and embryogenesis. All DEAD-box helicases contain several conserved sequence motifs within about 420 amino acids. These motifs include an A-type ATP binding motif, the DEAD-box/B-type ATP-binding motif, a serine/arginine/threonine tripeptide of unknown function, and a C-terminal glycine-rich motif with a possible role in substrate binding and unwinding. In addition, alignment of divergent DEAD-box helicase sequences has shown that 37 amino acid residues are identical

among these sequences, suggesting that conservation of these residues is important for helicase function. (Reviewed in Linder, P. et al. (1989) *Nature* 337:121-122.) Overexpression of the DEAD-box 1 protein (DDX1) may play a role in the progression of neuroblastoma (Nb) and retinoblastoma (Rb) tumors, suggesting that DDX1 may promote or enhance tumor progression by altering the normal secondary structure and expression levels of RNA in cancer cells. Other DEAD-box helicases have been implicated either directly or indirectly in ultraviolet light-induced tumors, B-cell lymphoma, and myeloid malignancies (Godbout, R. et al. (1998) *J. Biol. Chem.* 273:21161-21168).

Ribonucleases (RNases) catalyze the hydrolysis of phosphodiester bonds in RNA chains, thus cleaving the RNA. For example, RNase P is a ribonucleoprotein enzyme which cleaves the 5' end of pre-tRNAs as part of their maturation process. RNase H digests the RNA strand of an RNA/DNA hybrid, which occurs in cells invaded by retroviruses. RNase H is an important enzyme in the retroviral replication cycle. RNase H domains are often found associated with reverse transcriptases. RNase activity in serum and cell extracts is elevated in a variety of cancers and infectious diseases (Schein, C.H. (1997) *Nat. Biotechnol.* 15:529-536). Regulation of RNase activity may be a means for controlling tumor angiogenesis, allergic reactions, viral infection and replication, and fungal infections.

Translation

Proteins are translated from their RNA templates on the ribosome. The eukaryotic ribosome is composed of a 60S (large) subunit and a 40S (small) subunit, which together form the 80S ribosome. In addition to the 18S, 28S, 5S, and 5.8S rRNAs, the ribosome also contains more than fifty proteins. The ribosomal proteins have a prefix which denotes the subunit to which they belong, either L (large) or S (small). Three important sites are identified on the ribosome: i) the aminoacyl-tRNA site (A site) where charged tRNAs (except the initiator-tRNA) bind on arrival; ii) the peptidyl-tRNA site (P site) where new peptide bonds are formed and where the initiator tRNA binds, and iii) the exit site (E site) where deacylated tRNAs bind prior to their release from the ribosome (see Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY pp. 875-908; and Lodish, H. et al. (1995) Molecular Cell Biology Scientific American Books, New York NY pp. 119-138).

30 tRNA Charging

An important family of RNA-processing enzymes in the cytoplasm is the aminoacyl-transfer RNA (tRNA) synthetases. Protein biosynthesis depends on each amino acid forming a linkage with the appropriate tRNA. The aminoacyl-tRNA synthetases are responsible for correct attachment of an amino acid with its cognate tRNA. The 20 aminoacyl-tRNA synthetase enzymes

can be divided into two structural classes. each class characterized by a distinctive topology of the catalytic domain. Class I enzymes contain a catalytic domain based on the nucleotide-binding Rossman 'fold'. Class II enzymes contain a central catalytic domain, which consists of a seven-stranded antiparallel β -sheet motif, as well as N- and C- terminal regulatory domains. Class II enzymes are separated into two groups based on the heterodimeric or homodimeric structure of the enzyme; the latter group is further subdivided by the structure of the N- and C-terminal regulatory domains. (Hartlein, M. and Cusack, S. (1995) J. Mol. Evol. 40:519-530.)

One of the best studied of the aminoacyl-tRNA synthetases is seryl-tRNA synthetase (SerRS). SerRS is a class II enzyme with an N-terminal regulatory domain in the form of a solvent exposed, antiparallel coiled-coil (the "helical arm"). A multiple sequence alignment and similarity plot of SerRS enzymes from prokaryotes, such as *E. coli*, and eukaryotes, such as yeast and mice, demonstrate the greatest variability in the N-terminal helical arm domain. Eukaryotic SerRS enzymes also contain a 20-48 amino acid C-terminal extension not found in prokaryotic synthetases. Truncation of the N-terminal helical arm causes SerRS to lose specificity for serine-tRNA, such that the truncated SerRS reacts with non-cognate tRNAs as well. In eukaryotes, loss of the C-terminal sequence does not have a major affect on enzymatic activity. (Hartlein, *supra*; and Weygand-Durašević, I. et al. (1996) J. Biol. Chem. 271:2455-2461.)

Autoantibodies against aminoacyl-tRNAs are generated by patients with dermatomyositis and polymyositis, and correlate strongly with complicating interstitial lung disease (ILD). These antibodies appear to be generated in response to viral infection, and coxsackie virus has been used to induce experimental viral myositis in animals.

Translation Initiation

Initiation of translation can be divided into three stages. First an initiator transfer RNA (Met-tRNA_i) joins the 40S ribosomal subunit to form the 43S preinitiation complex. Next the 43S preinitiation complex binds the mRNA, and migrates to the correct AUG initiation codon. In the third step, the 60S ribosomal subunit joins the 40S subunit to generate an 80S ribosome at the initiation codon. Regulation of translation primarily involves the first and second stage in the initiation process (V.M. Pain (1996) Eur. J. Biochem. 236:747-771).

Several initiation factors, many of which contain multiple subunits, are involved in bringing an initiator tRNA and 40S ribosomal subunit together. eIF2B, a guanine nucleotide exchange protein, converts eIF2 from its GDP-bound inactive form to its GTP-bound active form. eIF2, a guanine nucleotide binding protein, recruits the initiator tRNA, bound to GTP, to the 40S ribosomal subunit. Two other factors, eIF1A and eIF3, bind and stabilize the 40S subunit by interacting with 18S ribosomal RNA and specific ribosomal structural proteins. eIF3 is also

involved in association of the 40S ribosomal subunit with mRNA. The Met-tRNA_i, eIF1A, eIF3, and 40S ribosomal subunit together make up the 43S preinitiation complex (Pain, supra).

Additional factors are required for binding of the 43S preinitiation complex to an mRNA molecule, and the process is regulated at several levels. eIF4F is a complex consisting of three
5 proteins: eIF4E, eIF4A, and eIF4G. eIF4E recognizes and binds to the mRNA 5'-terminal m⁷GTP cap, eIF4A is a bidirectional RNA-dependent helicase, and eIF4G is a scaffolding polypeptide. eIF4G has three binding domains. The N-terminal third of eIF4G interacts with eIF4E, the central third interacts with eIF4A, and the C-terminal third interacts with eIF3 bound to the 43S preinitiation complex. Thus, eIF4G acts as a bridge between the 40S ribosomal subunit and the
10 mRNA (M.W. Hentze (1997) Science 275:500-501).

The ability of eIF4F to initiate binding of the 43S preinitiation complex is regulated by two structural features of the mRNA. The mRNA molecule has an untranslated region (UTR) between the 5' cap and the AUG start codon. In some mRNAs this region forms secondary structures that impede binding of the 43S preinitiation complex. Interestingly, the group of
15 mRNAs possessing highly structured 5' UTRs includes a disproportionately high number of mRNAs encoding proteins that take part in or regulate processes involved in cell proliferation. The efficiency with which these mRNAs are translated may play a crucial role in the maintenance of correct restraints on cell growth. Additionally, regulatory proteins may bind to sites within the 5' UTR and stabilize this secondary structure to prevent translation. The helicase activity of eIF4A
20 is thought to function in removing this secondary structure to facilitate binding of the 43S preinitiation complex (Pain, supra).

The second structural feature of mRNA regulating binding of the 43S preinitiation complex is the 3' poly(A) tail. The translational efficiency of an mRNA is related to the length of its poly(A) tail, such that the longer the tail the more efficient the translation of the message. This
25 is due to an interaction between a protein that binds the poly(A) tail, the poly(A)-binding protein (PABP), and eIF4G. This interaction between PABP and eIF4G can only occur in the presence of RNA and involves a <120 amino acid site in the C-terminal half of eIF4G. This is an important form of regulation in translation of maternally-derived messages in early embryogenesis. The egg contains numerous mRNA molecules. Molecules with long poly(A) tails are translated early in
30 development and then undergo poly(A) tail shortening to repress further translation. Messages with short poly(A) tails, which are initially left untranslated, go through a cytoplasmic tail elongation to initiate translation later in development. This process of tail length modification responds to developmental cues and also appears to involve PABP (Pain, supra).

Another level of regulation involving eIF4G has been demonstrated by infection of

mammalian cells with picornaviruses. Several members of the picornavirus family, including poliovirus, human rhinovirus 2, and foot-and-mouth disease virus, inhibit cellular mRNA translation by cleaving eIF4G into two fragments. This cleavage by the viral protease effectively separates the N-terminal eIF4E binding site from the C-terminal binding sites for eIF4A, eIF3, and PABP. Picornavirus RNAs, which are uncapped, utilize the C-terminal fragment of eIF4G for translation. This C-terminal fragment contains a region that interacts, either directly or indirectly, with an internal ribosome entry site (IRES) on the viral RNA molecule. Thus, eIF4G acts as a bridge between the 40S ribosome and the viral IRES for cap-independent translation as well (Hentze, supra).

Recently, a protein (p97) in yeast was shown to resemble the C-terminal fragment of eIF4G produced by picornavirus protease cleavage. p97 binds to both eIF3 and eIF4A, and may be involved in cap-independent translation of cellular mRNAs, though no candidate RNA species have been found within eukaryotic cells. p97 has been shown to be involved in modulating γ -interferon-induced programmed cell death (Hentze, supra).

15 Translation Elongation

Elongation, the joining of additional amino acids to the initiator methionine to complete the polypeptide chain, involves elongation factors EF1 α , EF1 β γ , and EF2. EF1 α is a GTP-binding protein which, when bound by GTP, brings an aminoacyl-tRNA to the ribosome's A site. The amino acid attached to the newly arrived aminoacyl-tRNA forms a peptide bond with the initiator methionine. The GTP on EF1 α is hydrolyzed to GDP, and EF1 α -GDP dissociates from the ribosome. EF1 β γ binds EF1 α -GDP and induces the dissociation of GDP from EF1 α , allowing EF1 α to bind GTP and a new cycle to begin.

As subsequent aminoacyl-tRNAs are brought to the ribosome, EF-G, another GTP-binding protein, catalyzes the translocation of tRNAs from the A site to the P site and finally to the E site of the ribosome.

25 Translation Termination

The release factor eRF carries out termination of translation. eRF recognizes stop codons in the mRNA, leading to the release of the polypeptide chain from the ribosome.

The discovery of new RNA-associated proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, immune/inflammatory, and reproductive disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, RNA-associated proteins,

referred to collectively as "RNAAP" and individually as "RNAAP-1," "RNAAP-2," "RNAAP-3," "RNAAP-4," "RNAAP-5," "RNAAP-6," "RNAAP-7," "RNAAP-8," "RNAAP-9," "RNAAP-10," "RNAAP-11," "RNAAP-12," "RNAAP-13," "RNAAP-14," "RNAAP-15," "RNAAP-16," and "RNAAP-17." In one aspect, the invention provides a substantially purified polypeptide
5 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17, and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides an isolated and purified
10 polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

15 Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino
20 acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the
25 hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at
30 least 70% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. In another aspect, the expression vector is contained within a host cell.

5 The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

15 The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of RNAAP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

20 The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of RNAAP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

25

BRIEF DESCRIPTION OF FIGURES AND TABLES

Figure 1 shows the amino acid sequence alignment between RNAAP-1 (Incyte Clone number 399781; SEQ ID NO:1) and the human TLS-associated protein TASR (GI 2961149; SEQ ID NO:35), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

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Figures 2A-H show the amino acid sequence alignment between RNAAP-2 (1252206; SEQ ID NO:2) and human eIF4G1 (GI 2660712; SEQ ID NO:36), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 3A and 3B show the hydropathy plots of RNAAP-2 (1252206; SEQ ID NO:2) and

human eIF4G1 (GI 2660712; SEQ ID NO:36), respectively. Plots were produced using MACDNASIS PRO software (Hitachi Software Engineering, S. San Francisco CA).

Figures 4A and 4B show the amino acid sequence alignment between RNAAP-3 (2950994; SEQ ID NO:3) and Drosophila seryl-tRNA synthetase (GI 2440051; SEQ ID NO:37),
5 produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 5A-C show the amino acid sequence alignment between RNAAP-4 (3461657; SEQ ID NO:4) and human arginine methyltransferase (GI 1808648; SEQ ID NO:38), produced using the multisequence alignment program of LASERGENE software.

10 Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding RNAAP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods and algorithms used for identification of RNAAP.

15 Table 3 shows useful fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA
20 clones encoding RNAAP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze RNAAP, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

25 Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

30 It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

10 DEFINITIONS

"RNAAP" refers to the amino acid sequences of substantially purified RNAAP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

15 The term "agonist" refers to a molecule which, when bound to RNAAP, increases or prolongs the duration of the effect of RNAAP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of RNAAP.

An "allelic variant" is an alternative form of the gene encoding RNAAP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

25 "Altered" nucleic acid sequences encoding RNAAP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as RNAAP or a polypeptide with at least one functional characteristic of RNAAP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding RNAAP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding RNAAP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent RNAAP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity,

hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of RNAAP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values
5 may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic
10 fragments" refer to fragments of RNAAP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of RNAAP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated
15 with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which, when bound to RNAAP, decreases the
20 amount or the duration of the effect of the biological or immunological activity of RNAAP. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of RNAAP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies
25 that bind RNAAP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin,
30 and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on

the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic RNAAP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding RNAAP or fragments of RNAAP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping

sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding RNAAP, by northern analysis is indicative of the presence of nucleic acids encoding RNAAP in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding RNAAP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR,

Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) Parameters for each method may be the default parameters provided by MEGALIGN or may be specified by the user. The clustal algorithm groups sequences into
5 clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity
10 between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

15 "Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely
20 resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A
25 hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide
30 sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which

may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

5 The term "modulate" refers to a change in the activity of RNAAP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of RNAAP.

 The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to
10 DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which comprise a region of unique polynucleotide sequence that specifically identifies
15 SEQ ID NO:18-34, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:18-34 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:18-34 from related polynucleotide sequences. A fragment of SEQ ID NO:18-34 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:18-34 and the region of SEQ ID
20 NO:18-34 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

 The terms "operably associated" and "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding
25 sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

30 The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

“Peptide nucleic acid” (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript
5 elongation, and may be pegylated to extend their lifespan in the cell.

The term “sample” is used in its broadest sense. A sample suspected of containing nucleic acids encoding RNAAP, or fragments thereof, or RNAAP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

10 The terms “specific binding” and “specifically binding” refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope “A,” the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a
15 reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term “stringent conditions” refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other
20 conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term “substantially purified” refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60%
25 free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A “substitution” refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

“Substrate” refers to any suitable rigid or semi-rigid support including membranes, filters,
30 chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

“Transformation” describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to

various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment.

- 5 The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

- A "variant" of RNAAP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

- The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to RNAAP. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

30 THE INVENTION

The invention is based on the discovery of new human RNA-associated proteins (RNAAP), the polynucleotides encoding RNAAP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, immune/inflammatory, and reproductive disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding RNAAP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each RNAAP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The clones in column 5 were used to assemble the consensus nucleotide sequence of each RNAAP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows the identity of each polypeptide; and column 7 shows analytical methods used to identify each polypeptide through sequence homology and protein motifs. The segment of RNAAP-1 from residue R51 through residue D60, corresponding to region BL00030B, received a score of 1118 on a strength of 1104, while the segment from residue L12 through residue F30, corresponding to region BL00030A, received a score of 1089 on a strength of 1095, and supported the presence of BL00030B with a *P* value less than 2.4×10^{-4} .

As shown in Figure 1, RNAAP-1 has chemical and structural similarity with the human TLS-associated protein, TASR (GI 2961149; SEQ ID NO:35). In particular, RNAAP-1 and TASR share 76% identity, including the RNA recognition motif.

As shown in Figures 2 A-H, RNAAP-2 has chemical and structural similarity with human eIF4G1 (GI 2660712; SEQ ID NO:36). In particular, RNAAP-2 and human eIF4G1 share 45% identity and have similar isoelectric points (5.23 and 5.04, respectively). As shown in Figures 3A and 3B, RNAAP-2 and human eIF4G1 have similar hydrophobicity profiles.

As shown in Figures 4A and 4B, RNAAP-3 has chemical and structural similarity with *Drosophila* seryl-tRNA synthetase (GI 2440051; SEQ ID NO:37). In particular, RNAAP-3 and seryl-tRNA synthetase share 41% identity.

As shown in Figures 5A, 5B, and 5C, RNAAP-4 has chemical and structural similarity with human arginine methyltransferase (GI 1808648; SEQ ID NO:38). In particular, RNAAP-4 and arginine methyltransferase share 46% identity.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding RNAAP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1.

These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:18-34 and to distinguish between SEQ ID NO:18-34 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express RNAAP as a fraction of total tissues expressing RNAAP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing RNAAP as a fraction of total tissues expressing RNAAP. Northern analysis shows the expression of SEQ ID NO:18 in various libraries, at least 51% of which are associated with cancer and at least 29% of which are associated with inflammation and the immune response. Of particular note is SEQ ID NO: 29, which is expressed in only 25 libraries, 10(40%) of which are associated with reproductive tissue and 17(76%) of which are associated with cell proliferative disorders. Column 5 lists the vectors used to subclone each cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding RNAAP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The invention also encompasses RNAAP variants. A preferred RNAAP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the RNAAP amino acid sequence, and which contains at least one functional or structural characteristic of RNAAP.

The invention also encompasses polynucleotides which encode RNAAP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34, which encodes RNAAP.

The invention also encompasses a variant of a polynucleotide sequence encoding RNAAP. In particular, such a variant polynucleotide sequence will have at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding RNAAP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34 which has at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:18-34. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of RNAAP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the

genetic code, a multitude of polynucleotide sequences encoding RNAAP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring RNAAP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode RNAAP and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring RNAAP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding RNAAP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding RNAAP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode RNAAP and RNAAP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding RNAAP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:18-34 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and

most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 µg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art.

(See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding RNAAP may be extended utilizing a partial
5 nucleotide sequence and employing various PCR-based methods known in the art to detect
upstream sequences, such as promoters and regulatory elements. For example, one method which
may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown
sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods*
Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent
10 directions to amplify unknown sequence from a circularized template. The template is derived
from restriction fragments comprising a known genomic locus and surrounding sequences. (See,
e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves
PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial
chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In
15 this method, multiple restriction enzyme digestions and ligations may be used to insert an
engineered double-stranded sequence into a region of unknown sequence before performing PCR.
Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g.,
Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-306). Additionally, one may use PCR,
nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic
20 DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon
junctions. For all PCR-based methods, primers may be designed using commercially available
software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or
another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of
about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

25 When screening for full-length cDNAs, it is preferable to use libraries that have been
size-selected to include larger cDNAs. In addition, random-primed libraries, which often include
sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T)
library does not yield a full-length cDNA. Genomic libraries may be useful for extension of
sequence into 5' non-transcribed regulatory regions.

30 Capillary electrophoresis systems which are commercially available may be used to
analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular,
capillary sequencing may employ flowable polymers for electrophoretic separation, four different
nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for
detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal

using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

5 In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode RNAAP may be cloned in recombinant DNA molecules that direct expression of RNAAP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express
10 RNAAP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter RNAAP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments
15 and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding RNAAP may be synthesized, in whole or in
20 part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 7:215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 7:225-232.) Alternatively, RNAAP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis
25 may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of RNAAP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid
30 chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active RNAAP, the nucleotide sequences encoding

RNAAP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding RNAAP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding RNAAP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding RNAAP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding RNAAP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding RNAAP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding RNAAP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding RNAAP can

be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding RNAAP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these
5 vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of RNAAP are needed, e.g. for the production of antibodies, vectors which direct high level expression of RNAAP may be used. For example, vectors containing the strong, inducible T5 or T7
10 bacteriophage promoter may be used.

Yeast expression systems may be used for production of RNAAP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable
15 integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of RNAAP. Transcription of sequences encoding RNAAP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used
20 alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA
25 transformation or pathogen-mediated transfection. (See, e.g., *The McGraw Hill Yearbook of Science and Technology* (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding RNAAP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite
30 leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses RNAAP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat.

5 Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of RNAAP in cell lines is preferred. For example, sequences encoding RNAAP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate
10 vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

15 Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* or *apr* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers
20 resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g.,
25 Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol.
30 Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding RNAAP is inserted within a marker gene sequence, transformed cells containing sequences encoding RNAAP can be identified by the absence of

marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding RNAAP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding RNAAP and that
5 express RNAAP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

10 Immunological methods for detecting and measuring the expression of RNAAP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on RNAAP is preferred,
15 but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

20 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding RNAAP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding RNAAP, or any fragments thereof, may be
25 cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter
30 molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding RNAAP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The

protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode RNAAP may be designed to contain signal sequences which direct secretion of RNAAP through a prokaryotic or eukaryotic cell membrane.

- 5 In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity.
- 10 Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas, VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

- In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding RNAAP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric RNAAP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of RNAAP activity.
- 15 Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and
- 25 hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the RNAAP encoding sequence and the heterologous protein sequence, so that RNAAP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein
- 30 expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled RNAAP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems

(Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S -methionine.

Fragments of RNAAP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, *supra*, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of RNAAP may be synthesized separately and then combined to produce the full length molecule.

10 THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of RNAAP and RNA-associated proteins. In addition, the expression of RNAAP is closely associated with reproductive tissues, nervous tissues, cell proliferation including cancer, and inflammation and immune response. Therefore, RNAAP appears to play a role in cell proliferative, immune/inflammatory, and reproductive disorders. In the treatment of disorders associated with increased RNAAP expression or activity, it is desirable to decrease the expression or activity of RNAAP. In the treatment of the above conditions associated with decreased RNAAP expression or activity, it is desirable to increase the expression or activity of RNAAP.

Therefore, in one embodiment, RNAAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of RNAAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes

mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a reproductive disorder such as disorders of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis; disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia.

In another embodiment, a vector capable of expressing RNAAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of RNAAP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified RNAAP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of RNAAP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of RNAAP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of RNAAP including, but not limited to, those listed above.

In a further embodiment, an antagonist of RNAAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of RNAAP. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds RNAAP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express RNAAP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding RNAAP may be administered to a subject to treat or prevent a disorder associated with

increased expression or activity of RNAAP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination
5 therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

10 An antagonist of RNAAP may be produced using methods which are generally known in the art. In particular, purified RNAAP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind RNAAP. Antibodies to RNAAP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab
15 fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with RNAAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various
20 adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

25 It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to RNAAP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of
30 RNAAP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to RNAAP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-

hybridoma technique. (See, e.g., Kohler, G. et al. (1975) *Nature* 256:495-497; Kozbor, D. et al. (1985) *J. Immunol. Methods* 81:31-42; Cote, R.J. et al. (1983) *Proc. Natl. Acad. Sci.* 80:2026-2030; and Cole, S.P. et al. (1984) *Mol. Cell Biol.* 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the
5 splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate
antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984)
Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) *Nature* 312:604-608; and
Takeda, S. et al. (1985) *Nature* 314:452-454.) Alternatively, techniques described for the
production of single chain antibodies may be adapted, using methods known in the art, to produce
10 RNAAP-specific single chain antibodies. Antibodies with related specificity, but of distinct
idiotypic composition, may be generated by chain shuffling from random combinatorial
immunoglobulin libraries. (See, e.g., Burton D.R. (1991) *Proc. Natl. Acad. Sci.* 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte
population or by screening immunoglobulin libraries or panels of highly specific binding reagents
15 as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) *Proc. Natl. Acad. Sci.* 86:
3833-3837; Winter, G. et al. (1991) *Nature* 349:293-299.)

Antibody fragments which contain specific binding sites for RNAAP may also be
generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments
produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing
20 the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be
constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired
specificity. (See, e.g., Huse, W.D. et al. (1989) *Science* 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the
desired specificity. Numerous protocols for competitive binding or immunoradiometric assays
25 using either polyclonal or monoclonal antibodies with established specificities are well known in
the art. Such immunoassays typically involve the measurement of complex formation between
RNAAP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing
monoclonal antibodies reactive to two non-interfering RNAAP epitopes is preferred, but a
competitive binding assay may also be employed (Pound, supra).

30 Various methods such as Scatchard analysis in conjunction with radioimmunoassay
techniques may be used to assess the affinity of antibodies for RNAAP. Affinity is expressed as
an association constant, K_a , which is defined as the molar concentration of RNAAP-antibody
complex divided by the molar concentrations of free antigen and free antibody under equilibrium
conditions. The K_a determined for a preparation of polyclonal antibodies, which are

heterogeneous in their affinities for multiple RNAAP epitopes, represents the average affinity, or avidity, of the antibodies for RNAAP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular RNAAP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the RNAAP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of RNAAP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of RNAAP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding RNAAP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding RNAAP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding RNAAP. Thus, complementary molecules or fragments may be used to modulate RNAAP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding RNAAP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding RNAAP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding RNAAP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding RNAAP.

Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding RNAAP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred.

Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding RNAAP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding RNAAP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or

SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of RNAAP, antibodies to RNAAP, and mimetics, agonists, antagonists, or inhibitors of RNAAP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which

facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using
5 pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active
10 compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums,
15 including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel,
20 polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol.
25 Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in
30 aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include

fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

5 For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

10 The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2%
15 sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of RNAAP, such labeling would include amount, frequency, and method of administration.

20 Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in
25 cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example
30 RNAAP or fragments thereof, antibodies of RNAAP, and agonists, antagonists or inhibitors of RNAAP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic

effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about $0.1 \mu\text{g}$ to $100,000 \mu\text{g}$, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind RNAAP may be used for the diagnosis of disorders characterized by expression of RNAAP, or in assays to monitor patients being treated with RNAAP or agonists, antagonists, or inhibitors of RNAAP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for RNAAP include methods which utilize the antibody and a label to detect RNAAP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring RNAAP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of RNAAP expression. Normal or standard values for RNAAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to

RNAAP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of RNAAP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding RNAAP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of RNAAP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of RNAAP, and to monitor regulation of RNAAP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding RNAAP or closely related molecules may be used to identify nucleic acid sequences which encode RNAAP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding RNAAP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the RNAAP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:18-34 or from genomic sequences including promoters, enhancers, and introns of the RNAAP gene.

Means for producing specific hybridization probes for DNAs encoding RNAAP include the cloning of polynucleotide sequences encoding RNAAP or RNAAP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding RNAAP may be used for the diagnosis of disorders associated with expression of RNAAP. Examples of such disorders include, but are not limited to,

a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a reproductive disorder such as disorders of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis; disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia. The polynucleotide sequences encoding RNAAP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered RNAAP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding RNAAP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The

nucleotide sequences encoding RNAAP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding RNAAP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of RNAAP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding RNAAP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding RNAAP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced *in vitro*. Oligomers will preferably contain a fragment of a polynucleotide encoding RNAAP, or a fragment of a polynucleotide complementary to the polynucleotide encoding RNAAP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less

stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of RNAAP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

10 In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

15 Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

20 In another embodiment of the invention, nucleic acid sequences encoding RNAAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial
25 P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in
30 Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding RNAAP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene

sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, RNAAP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between RNAAP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with RNAAP, or fragments thereof, and washed. Bound RNAAP is then detected by methods well known in the art. Purified RNAAP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding RNAAP specifically compete with a test compound for binding RNAAP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with RNAAP.

In additional embodiments, the nucleotide sequences which encode RNAAP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5 The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No. PF-0598 P, filed September 22, 1998], U.S. Ser. No. [Attorney Docket No. PF-0600 P, filed September 17, 1998], U.S. Ser. No. [Attorney Docket No. PF-0626 P, filed November 4, 1998], and U.S. Ser. No. 60/128,660, are hereby expressly incorporated by reference.

10 EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life
15 Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA
20 purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

25 In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random
30 primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the

polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies. II.

5 Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those

skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:18-34. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7;

Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the
5 sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the
10 length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in
15 which the transcript encoding RNAAP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number
20 of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of RNAAP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:18-34 were produced by extension
25 of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal
30 to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art.

PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

10 The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For 20 shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in 25 restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following 30 parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer

sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:18-34 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:18-34 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ - 32 P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography and compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, *supra*.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected

using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g.,
5 UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

10 Sequences complementary to the RNAAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring RNAAP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of
15 RNAAP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the RNAAP-encoding transcript.

IX. Expression of RNAAP

20 Expression and purification of RNAAP is achieved using bacterial or virus-based expression systems. For expression of RNAAP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac*
25 operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express RNAAP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of RNAAP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin
30 gene of baculovirus is replaced with cDNA encoding RNAAP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional

genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, RNAAP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from RNAAP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified RNAAP obtained by these methods can be used directly in the following activity assay.

15 X. Demonstration of RNAAP Activity

RNAAP activity is demonstrated by a polyacrylamide gel mobility-shift assay. In preparation for this assay, RNAAP is expressed by transforming a mammalian cell line such as COS7, HeLa or CHO with a eukaryotic expression vector containing RNAAP cDNA. The cells are incubated for 48-72 hours after transformation under conditions appropriate for the cell line to allow expression and accumulation of RNAAP. Extracts containing solubilized proteins can be prepared from cells expressing RNAAP by methods well known in the art. Portions of the extract containing RNAAP are added to [³²P]-labeled RNA. Radioactive RNA can be synthesized in vitro by techniques well known in the art. The mixtures are incubated at 25°C in the presence of RNase inhibitors under buffered conditions for 5-10 minutes. After incubation, the samples are analyzed by polyacrylamide gel electrophoresis followed by autoradiography. The presence of a band on the autoradiogram indicates the formation of a complex between RNAAP and the radioactive transcript. A band of similar mobility will be absent in samples prepared using control extracts prepared from untransformed cells.

Alternatively, the activity of RNAAP is measured as the level of in vitro translation of cap-dependent chloramphenicol acetyltransferase (CAT) and cap-independent luciferase (LUC) reporter constructs (Haghighat, A., et al. (1996) J. Virol. 70:8444-8450). Bicistronic pGEMCAT/EMC/LUC mRNA is used in the assay. The first cistron on this mRNA construct encodes the CAT protein and its translation is cap-dependent. The second cistron encodes luciferase enzyme. The encoded region of the second cistron is preceded by the IRES of

encephalomyocarditis (EMC) virus, making luciferase translation cap independent. Linearized pGEMCAT/EMC/LUC is transcribed in vitro using T7 RNA polymerase in the presence of 10-fold molar excess m⁷GpppG, a cap analog that promotes capping of the RNA product. Rabbit reticulocyte lysate is treated with picornavirus 2A protease. Treatment of the lysate with 2A protease reduces cap-dependent (CAT) translation, but does not inhibit cap-independent (luciferase) translation. Treated lysate is programmed by addition of the capped mRNA in the presence of 20 µCi [³⁵S]methionine. Translation reaction mixtures are incubated for 90 min in the presence of added eIF4E, RNAAP, eIF4E and RNAAP, or with no additions. Translation products are analyzed by SDS-PAGE, acid fixation, and autoradiography. RNAAP activity is calculated based on the expression level of CAT relative to luciferase as compared to control reactions lacking RNAAP.

Alternatively, RNAAP activity is measured as the aminoacylation of a substrate tRNA in the presence of [¹⁴C]serine. RNAAP is incubated with tRNA^{ser} and [¹⁴C]serine in a buffered solution. ¹⁴C-labeled product is separated from free [¹⁴C]serine by chromatography, and the incorporated ¹⁴C is quantified by scintillation counter. The amount of ¹⁴C detected is proportional to the activity of RNAAP in this assay.

Alternatively, RNAAP activity is measured as the methylation of a substrate in the presence of [methyl-³H]-S-adenosylmethionine (SAM). RNAAP is incubated with an appropriate substrate and [methyl-³H]SAM in a buffered solution. ³H-labeled product is separated from free [methyl-³H]SAM by gel electrophoresis, and the incorporated ³H is quantified by fluorography. The amount of ³H detected is proportional to the activity of RNAAP in this assay.

XI. Functional Assays

RNAAP function is assessed by expressing the sequences encoding RNAAP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion

protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of RNAAP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding RNAAP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding RNAAP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of RNAAP Specific Antibodies

RNAAP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the RNAAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit

antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring RNAAP Using Specific Antibodies

Naturally occurring or recombinant RNAAP is substantially purified by immunoaffinity chromatography using antibodies specific for RNAAP. An immunoaffinity column is constructed
5 by covalently coupling anti-RNAAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing RNAAP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of RNAAP (e.g., high ionic
10 strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/RNAAP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and RNAAP is collected.

XIV. Identification of Molecules Which Interact with RNAAP

RNAAP, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter
15 reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled RNAAP, washed, and any wells with labeled RNAAP complex are assayed. Data obtained using different concentrations of RNAAP are used to calculate values for the number, affinity, and association of RNAAP with the candidate molecules.

20 Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying
25 out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	18	399781	PITUNOT02	399781H1 and 399781X12 (PITUNOT02), 1271965F6 (TESTTUT02), 790764R1 and 792124R1 (PROSTUT03), and 405935R1 (EOSIHET02)
2	19	1252206	LUNGFET03	1232931T6 (LUNGFET03), 3109423H1 (BRSTTUT15), 3113355H1 (BRSTNOT17), 3330287H1 (HEAONOT04), 3269650H1 (BRAINOT20), 1662596H1 (BRSTNOT09), 2655078H1 (THYMNOT04), 2266829H1 and 2266829R6 (UTRSNOT02), 4333545H1 (KIDCTMT01), 1595462F6 (BRAINOT14), 078192R1 and 078192F1 (SYNORAB01), 4836680H1 (BRAUNOT01), 1252206F6 (LUNGFET03), 1638473F6 (UTRSNOT06), SAJA00661R1, SAJA00355F1, SAJA01106R1, SAJA01874F1, and SAJA02468F1
3	20	2950994	KIDNFET01	1968448H1 (BRSTNOT04), 1435425T6 (PANCNOT08), 808869T1 (LUNGNOT04), 2795721F6 (NPOLNOT01), and 2950994H1 (KIDNFET01)
4	21	3461657	293TF201	2606248F6 (LUNGTUT07), 2052041X301D1 (LIVRFET02), 4341820F6 (BRAUNOT02), 2789769F6 (COLNTUT16), 3461657H1 (293TF2T01), SBUA03574D1 and SBUA00296D1
5	22	053076	FIBRNOT01	053076H1 (FIBRNOT01), 534171F1 (BRAINOT03), 4717220H1 (BRAIHCT02)
6	23	1292379	PGANNOT03	458715T6 (KERANOT01), 850050T1 (NGANNOT01), 1292379F1, 1292379H1 and 1292379T1 (PGANNOT03), 1398840F6 and 1398840T6 (BRAITUT08), 3447383H2 (BLADNOT09), 3780263H1 (BRSTNOT27)
7	24	1437783	PANCNOT08	117781F1 (KIDNNOT01), 1352071F1 (LATRTUT02), 1437783H1 (PANCNOT08), 2527706H1 (GBLANOT02), 4567705H1 (HELATXT01)
8	25	1557635	BLADTUT04	077627R1 (SYNORAB01), 1557635F1 and 1557635H1 (BLADTUT04), 1568446F1 (UTRSNOT05), 1901128F6 (BLADTUT06), 2013353T6 (TESTNOT03), 2098109H1 (BRAITUT02), 2568583T6 (HIPOAZT01), 3866538H1 (BRAITUT07)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
9	26	20493352	LIVRFET02	078075R1 (SYNORAB01), 994247R6 (COLNNOT11), 1334674F6 (COLNNOT13), 2049352F6 and 2049352H1 (LIVRFET02), 3219182H1 (COLNNON03)
10	27	2231663	PROSNOT16	307827H1 (HEARNOT01), 1455948F1 and 1455948R1 (COLNFET02), 2231663H1 (PROSNOT16), 3779128H1 (BRSTNOT27)
11	28	2604449	LUNGTUT07	606296R6 (BRSTTUT01), 1718568T6 (BLADNOT06), 2604449F6 and 2604449H1 (LUNGTUT07), 5093027F6 (UTRSTMR01), SAEA01050F1, SAEA01365F1, SAEC11108F1, SBKA00681F1
12	29	2604993	LUNGTUT07	1441072F6 and 1441072T6 (THYRNOT03), 2604993H1 (LUNGTUT07), 3389190T6 (LUNGTUT17), SBIA05937D1, SBIA11687D1, SBIA04881D1, SBIA03937D1, SBIA00985D1
13	30	2879070	UTRSTUT05	1458387F7, 1458387R1, and 1458387T6 (COLNFET02), 1858014X13C1 and 1858014X14C1 (PROSNOT18), 2595610H1 (OVRTUT02), 2879070H1 (UTRSTUT05)
14	31	3093845	BRSTNOT19	134421R1 (BMARNOT02), 979683R6 (TONGTUT01), 3093845F6 and 3093845H1 (BRSTNOT19), 3294785F6 (TLYJINT01)
15	32	3685685	HEARNOT01	1556450F1 (BLADTUT04), 1615712T6 (BRAITUT12), 2041291R6 (HIPONON02), 2448460F6 (THPINOT03), 3685685H1 (HEARNOT01), 3954790H1 (PONSAT01), 4918977H2 (TESTNOT11)
16	33	3825977	BRAINOT23	2373839T6 and 2375912X302D1 (ISLTNOT01), 3825977H1 (BRAINOT23), 3882790H1 (SPLNNOT11), SBIA02579D1, SBIA02994D1, SBIA10082D1, SBIA06183D1, SBIA05526D1, SBIA02807D1
17	34	4941262	BRAIFEN03	4941262F6 and 4941262H1 (BRAIFEN03)

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation on Sites	Signature Sequence	Identification	Analytical Methods
1	216	S129, T21, S108, T161, T178, T47, S107, S143, T150, S185, Y116, Y138	N9	RNA recognition motif: L12-I83 RNA-binding region RNP-1 R51 signature: R1- D60, L12-F30	GI 2961149 Human TLS- associated protein, TASR	Motifs BLAST PFAM BLOCKS
2	1584	S740, S888, S965, S257, T294, S304, S317, S366, S370, T517, S542, S582, S584, S598, T615, S718, S865, T1058, S1085, T1115, S1155, S1164, T1190, S1209, S1217, S1227, S1264, S1290, S1333, S1381, S1416, S1421, S1501, T1503, S1550, S30, T141, S304, S362, S456, S491, T507, S611, S700, S718, S735, T817, S965, S985, S1121, T1126, T1144, S1155, T1175, S1200, S1286, S1333, S1367, S1381, S1416, T1480, S1550	N1162, N1188, N1195	Leucine zipper pattern: L1513- L1534 Wilm's tumor protein: G80- P94, S412-H426	GI 2660712 Human eIF4G1	Motifs BLAST PRINTS

Table 2 (cont.)

Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
3	166	S78, T135	N72, N99		GI 2440051 seryl-tRNA synthetase	BLAST
4	531	S27, T58, S59, S157, S242, S339, S428, S430, S242, T439, S475, S492, Y89	N155, N522, N523	C2H2 type zinc finger motif: C50-H71 N-methyltransferase cofactor-binding motif: V259-A273	GI 1808648 Human arginine methyltransferase	Motifs BLAST BLOCKS PFAM PRINTS
5	148	S32 S38 S47 T69 T141 Y60		A31-D115 (Ribosomal L27 protein) M1-A27 (Signal peptide)	ribosomal protein L27 g 642605	Motifs BLAST Pfam HMM SPScan
6	317	S20 S40 S106 S110 S117 T135 T142 S144 T260 S302 S6 S10 T134 S215 S281	N148 N208 N228		pre-ribosomal particle assembly protein g 2398808	Motifs BLAST
7	278	T10 S83 S56 T57 T61 T121 S202 S244 T13 T68 T156 T192 S224 Y251	N71 N120		translation initiation factor 3 (infC) g 3844793	Motifs BLAST

Table 2 (cont.)

Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
8	586	T29 T81 T261 S512 T4 S21 T29 S97 S227 T229 S235 T348 S371 S417 T475 T485 S511 S513 S515 S554 T562 S77 T127 T194 S206 S215 S256 S356 S479 Y274 Y297 Y309	N427		Similar to mRNA splicing factor g 3878326	Motifs BLAST
9	384	T32 S167 T327 T339 T349 S28 T148 T311 S372 Y13 Y19 Y86 Y277	N229	H257-M296 (Cytidine and deoxycytidylate deaminases zinc-binding region signature)	phorbolin I protein kinase C associated protein g 436941	Motifs BLAST
10	325	T61 S298 S320 S49 T53 S116	N163	R94-G302 (L1P family ribosomal proteins)	Ribonucleotide reductase subunit M2 g 200768	Motifs BLAST Pfam

Table 2 (cont.)

Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
11	351	S39 T182 S329 S18 S29 T65 T182 S225 S38 Y87	N23 N314	E131-I146 (Ribonucleotide reductase small subunit) P46-D100, F123-D148, F198-F239, V251-R292 (Ribonucleotide reductase) W69-Y331 (Ribonucleotide reductase) R186-W207 (transmembrane)	Ribonucleotide reductase subunit M2 g 200468	Motifs BLAST Pfam BLOCKS HMM
12	681	T68 S79 S135 T160 S179 S201 S216 S237 T301 T312 T338 T363 T405 T457 S524 S123	N89 N600 N623	V227-V297, V328- L401, I447-V520 (RNA recognition motif) M1-K22 (signal peptide)	Similarity to Human heterogeneous nuclear ribonucleopro- tein(hnRNP) F protein g 3880146	Motifs BLAST Pfam SPScan
13	408	S3 S45 S68 T212 T236 S248 T145 T279 Y193	N206	I121-M144 (transmembrane)	RNA helicase A g2880057	Motifs BLAST HMM

Table 2 (cont.)

Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
14	351	S126 S5 T7 S75 S108 S140 S195 S314 S339 S59 S122 S254 S300 S344 Y23	N113 N202	K36-Y43 (Eukaryotic putative RNA-binding region RNP-1 signature) I2-L38, V127-V194, L269-V334 (RNA recognition motif)	Hel-N2 RNA binding protein g905387	Motifs BLAST Pfam
15	472	S69 S116 S346 S89 S237 S239 S301 T303 S358 S4 T39 S124 T176	N219 N248	102-130, 178-204 (glycosyl hydrolase)	Human RNA binding protein g 2804465	Motifs BLAST PRINTS
16	616	S154 S368 S376 T570 S14 S44 T53 S83 S94 S466		V18-V89 (RNA recognition motif) F36-R85 (eukaryotic RNA-binding RNP-1)	Cleavage stimulating factor g 181139	Motifs BLAST Pfam ProfileScan
17	112	T42 Y69		G74-P95 (ribosomal protein L35Ae signature) L12-F106 (ribosomal protein L35Ae signature)	g4392 ribosomal protein L37a	Motifs BLAST Pfam BLOCKS

Table 3

Polynucleotide SEQ ID NO:	Selected Fragment (Nucleotide number)	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
18	30-90	Nervous (0.191) Reproductive (0.309)	Cell proliferation (0.510) Inflammation and Immune Response (0.290)	PSPORT1
19	1137-1196	Nervous (0.245) Reproductive (0.216)	Cell proliferation (0.560) Inflammation and Immune Response (0.230)	pINCY
20	454-510	Reproductive (0.263) Nervous (0.211)	Cancer (0.580) Inflammation and Immune Response (0.160)	pINCY
21	31-81	Nervous (0.357) Gastrointestinal (0.179) Reproductive (0.143)	Cancer (0.610) Inflammation and Immune Response (0.210)	pINCY
22	1-46	Reproductive (0.247) Nervous (0.183) Gastrointestinal (0.118)	Cell proliferation (0.613) Inflammation (0.290)	PBLUESCRIPT
23	273-317	Reproductive (0.256) Nervous (0.209)	Cell proliferation (0.465) Inflammation (0.256)	pINCY
24	434-478	Gastrointestinal (0.244) Nervous (0.186) Reproductive (0.163)	Cell proliferation (0.535) Inflammation (0.361)	pINCY
25	174-218	Reproductive (0.230) Nervous (0.216) Cardiovascular (0.122)	Cell proliferation (0.554) Inflammation (0.311)	pINCY

26	489-533	Reproductive (0.270) Hematopoietic/Immune (0.243) Nervous (0.162)	Cell proliferation (0.676) Inflammation (0.405)	pINCY
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Table 3 (cont.)

Polynucleotide SEQ ID NO:	Selected Fragment (Nucleotide number)	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
27	199-252	Reproductive (0.308) Cardiovascular (0.205)	Cell proliferation (0.770) Inflammation (0.128)	pINCY
28	110-154	Cardiovascular (0.289) Nervous (0.184) Reproductive (0.158)	Cell proliferation (0.685) Inflammation (0.158)	pINCY
29	326-370	Reproductive (0.400) Gastrointestinal (0.240) Cardiovascular (0.120)	Cell proliferation (0.760) Inflammation (0.240)	pINCY
30	516-563	Reproductive (0.415) Nervous (0.151) Hematopoietic/Immune (0.113)	Cell proliferation (0.566) Inflammation (0.320)	pINCY
31	272-316	Hematopoietic/Immune (0.286) Gastrointestinal (0.214) Reproductive (0.214)	Inflammation (0.714) Cell proliferation (0.495)	pINCY
32	119-163	Reproductive (0.328) Hematopoietic/Immune (0.219) Nervous (0.156)	Cell proliferation (0.672) Inflammation (0.313)	pINCY
33	812-856	Gastrointestinal (0.208) Hematopoietic/Immune (0.208) Developmental (0.167) Nervous (0.167)	Inflammation (0.541) Cell proliferation (0.458)	pINCY
34	42-86	Nervous (1.000)	Cell proliferation (1.000)	pINCY

Table 4

Polynucleotide SEQ ID NO:	Library	Library Comment
18	PITUNOT02	Library was constructed using RNA isolated from the pituitary glands removed from a pool of 87 male and female donors, 15 to 75 years old (RNA acquired from Clontech, CLON 6584-1).
19	LUNGFET03	Library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation. Family history included bronchitis.
20	KIDNFET01	Library was constructed using RNA isolated from kidney tissue removed from a Caucasian female fetus, who died at 17 weeks' gestation from anencephalus.
21	293TF201	Library was constructed using RNA isolated from a treated, transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were treated with 5-aza-2'-deoxycytidine (5AZA) and transformed with adenovirus 5 DNA.
22	FIBRNOT01	Library was constructed using RNA isolated from the WI38 lung fibroblast cell line, which was derived from a 3-month-old Caucasian female fetus. 2×10^6 primary clones were then amplified to stabilize the library for long-term storage.
23	PGANNOT03	Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and was associated with a grade 2 renal cell carcinoma, clear cell type, which did not penetrate the capsule.
24	PANCNOT08	Library was constructed using RNA isolated from pancreatic tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology for the associated tumor tissue indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Family history included cardiovascular disease, type II diabetes, and stomach cancer.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
25	BLADTUT04	Library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. Family history included type I diabetes, malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and an acute myocardial infarction.
26	LIVRFET02	Library was constructed using RNA isolated from liver tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation. Family history included bronchitis.
27	PROSNOT16	Library was constructed using RNA isolated from diseased prostate tissue removed from a 68-year-old Caucasian male during a radical prostatectomy. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). The patient presented with elevated prostate specific antigen (PSA) and was diagnosed with myasthenia gravis. Patient history included osteoarthritis, and type II diabetes. Family history included benign hypertension, acute myocardial infarction, hyperlipidemia, and arteriosclerotic coronary artery disease.
28	LUNGTUT07	Library was constructed using RNA isolated from lung tumor tissue removed from the upper lobe of a 50-year-old Caucasian male during segmental lung resection. Pathology indicated an invasive grade 4 squamous cell adenocarcinoma. Patient history included tobacco use. Family history included skin cancer.
29	LUNGTUT07	Library was constructed using RNA isolated from lung tumor tissue removed from the upper lobe of a 50-year-old Caucasian male during segmental lung resection. Pathology indicated an invasive grade 4 squamous cell adenocarcinoma. Patient history included tobacco use. Family history included skin cancer.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
30	UTRSTUT05	Library was constructed using RNA isolated from uterine tumor tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated uterine leiomyoma. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Patient history included a ventral hernia and a benign ovarian neoplasm.
31	BRSTNOT19	Library was constructed using RNA isolated from breast tissue removed from a 67-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated residual invasive lobular carcinoma. The focus of residual invasive carcinoma was positive for both estrogen and progesterone. Patient history included depressive disorder and benign large bowel neoplasm. Family history included cerebrovascular disease, benign hypertension, congestive heart failure, and lung cancer.
32	HEAANOT01	Library was constructed using RNA isolated from right coronary and right circumflex coronary artery tissue removed from the explanted heart of a 46-year-old Caucasian male during a heart transplantation. Patient history included myocardial infarction from total occlusion of the left anterior descending coronary artery, atherosclerotic coronary artery disease, hyperlipidemia, myocardial ischemia, dilated cardiomyopathy, left ventricular dysfunction, and tobacco use. Family history included atherosclerotic coronary artery disease.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
33	BRAINOT23	Library was constructed using RNA isolated from right temporal lobe tissue removed from a 45-year-old Black male during a brain lobectomy. Pathology for the associated tumor tissue indicated dysembryoplastic neuroepithelial tumor of the right temporal lobe. The right temporal region dura was consistent with calcifying pseudotumor of the neuraxis. The patient presented with convulsive intractable epilepsy, partial epilepsy, and memory disturbance. Patient history included obesity, meningitis, backache, unspecified sleep apnea, acute stress reaction, acquired knee deformity, and chronic sinusitis. Family history included obesity, benign hypertension, cirrhosis of the liver, alcohol abuse, hyperlipidemia, cerebrovascular disease, and type II diabetes.
34	BRAIFEN03	This normalized fetal brain tissue library was constructed from 3.26 million independent clones from a fetal brain library. Starting RNA was made from brain tissue removed from a Caucasian male fetus with a hypoplastic left heart stillborn after 23 weeks' gestation. The library was normalized in two rounds (with 48 hour reannealing hybridizations) using conditions adapted from Soares et al. and Bonaldo et al.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value= 1.0E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value= 1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS and PRINTS databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score= 1000 or greater; Ratio of Score/Strength = 0.75 or larger; and Probability value= 1.0E-3 or less
PFAM	A Hidden Markov Models-based application useful for protein family search.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits, depending on individual protein families

Table 5 cont.

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score = 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score = 120 or greater; Match length = 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score = 5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <i>supra</i> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, and fragments thereof.
2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
7. A method for detecting a polynucleotide, the method comprising the steps of:
 - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ

ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, and fragments thereof.

10. An isolated and purified polynucleotide variant having at least 90%
5 polynucleotide sequence identity to the polynucleotide of claim 9.
 11. An isolated and purified polynucleotide having a sequence which is
complementary to the polynucleotide of claim 9.
 12. An expression vector comprising at least a fragment of the polynucleotide of
10 claim 3.
 13. A host cell comprising the expression vector of claim 12.
 14. A method for producing a polypeptide, the method comprising the steps of:
15 a) culturing the host cell of claim 13 under conditions suitable for the
expression of the polypeptide; and
b) recovering the polypeptide from the host cell culture.
 15. A pharmaceutical composition comprising the polypeptide of claim 1 in
20 conjunction with a suitable pharmaceutical carrier.
 16. A purified antibody which specifically binds to the polypeptide of claim 1.
 17. A purified agonist of the polypeptide of claim 1.
 - 25 18. A purified antagonist of the polypeptide of claim 1.
 19. A method for treating or preventing a disorder associated with decreased
expression or activity of RNAAP, the method comprising administering to a subject in need of
30 such treatment an effective amount of the pharmaceutical composition of claim 15.
 20. A method for treating or preventing a disorder associated with increased
expression or activity of RNAAP, the method comprising administering to a subject in need of
such treatment an effective amount of the antagonist of claim 18.

1/15

1	M S R Y L R P P N T S L F V R N V A D D T R S E D L R R E F	399781
1	M S R Y L R P P N T S L F V R N V A D D T R S E D L R R E F	GI 2961149
31	G R Y G P I V D V Y V P L D F Y T R R P P R G F A Y V Q F E D	399781
31	G R Y G P I V D V Y V P L D F Y T R R P P R G F A Y V Q F E D	GI 2961149
61	V R D A E D A L H N L D R K W I C G R Q I E I Q F A Q G D R	399781
61	V R D A E D A L H N L D R K W I C G R Q I E I Q F A Q G D R	GI 2961149
91	K T P N Q M K A K E G R N V Y S S S R Y D D Y D R Y R R S R	399781
91	K T P N Q M K A K E G R N V Y S S S R Y D D Y D R Y R R S R	GI 2961149
121	S R S Y E R R R S R S R S F D Y N Y R R S Y S P R N S R P T	399781
121	S R S Y E R R R S R S R S F D Y N Y R R S Y S P R N S R P T	GI 2961149
151	G R P R R R E A I P T M I D Q T A A G I P S T V L T T L Q	399781
151	G R P R R S -	GI 2961149
181	E R S E S G K R T K E G Q F K R P K G G W K V L Q Y E - - Y	399781
157	- R S H S D N - - - - - D R P N C S W N T - Q Y S S A Y	GI 2961149
209	C T N I L T L V	399781
178	Y T S - - R K I	GI 2961149

FIGURE 1

7/1/2007 TO

1

391 N P P E E M K L E C I P A P I T P S T V P S F P P T P P T P 1252206
224 F P P E F O A K E - - V T A S V A P P T I P S A T P A T A P S GI 2660712

FIGURE 2B

4/15

421	P A S P P H T P V I V P A A A T V S S P S A A I T V Q R V	1252206
252	A T S P A Q E E E M E E E E E E E G E A G E A G E A E S E	GI 2660712
451	L E E D E S I R T C L S E D A K E I Q N K I E V E A D G Q T	1252206
282	K G G E E L - - - L P P E S T P I P A N L - - - - -	GI 2660712
481	E E I L D S Q N L N S R R S P V P A Q I A I T V P K T W K K	1252206
300	- - - - - S Q N L E A - - - A A A T Q V A V S V P K R R K	GI 2660712
511	P K D R T R T E E M L E A E L E L K A E E E L S I D K V L	1252206
322	I K E L N K K - - E A V G D L L D A F K E A N P A V P E V -	GI 2660712
541	E S E Q D K M S Q G F H P E R D P S D L K K V K A V E E N G	1252206
349	- - - E N Q P P A G S N P G P E S E G - - - S G V P P R P	GI 2660712
571	E E A E P V R N G A E S - V S E G E G I D A N S G S T D S S	1252206
372	E E A D E T W D S K E D K I H N A E N I Q P G E Q K - - -	GI 2660712
600	G D G V T F P F K P E S W K P T D T E G K K Q Y D R E F F L L	1252206
398	- - - - - Y E Y K S D Q W K P P N L E E K K R Y D R E F F L L	GI 2660712

FIGURE 2C

630 D F Q F M P A C I Q K P E G L P P I S D V V L D K I N Q P K 1252206
 423 G F Q F I F A S M Q K P E G L P H I S D V V L D K A N - - K GI 2660712

 660 L P M R T L D P R I L P R - - - G P D F T P A F A D F G R Q 1252206
 451 T P L R P L D P T R L Q G I N C G P D F T P S F A N L G R T GI 2660712

 687 T P G G R G V P - - - - - - - L L N V G S R R S Q 1252206
 481 T L S T R G P P R G G P G G E L P R G P Q A G L G P R R S Q GI 2660712

 705 P G Q R R E P R K I I - T V S V K E D V H L K K A E N A W K 1252206
 511 Q G P R K E P R K I I A T V L M T E D I K L N K A E K A W K GI 2660712

 734 P S Q K R - - - - - D S Q A D D P E N I K T Q E L F R K V R 1252206
 541 P S S K R T A A D K D R G E E D A D G S K T Q D L F R R V R GI 2660712

 759 S I L N K L T P Q M F N Q L M K Q V S G L T V D T E E R L K 1252206
 571 S I L N K L T P Q M F Q Q L M K Q V T Q L A I D T E E R L K GI 2660712

 789 G V I D L V F E K A I D E P S F S V A Y A N M C R C L V T L 1252206
 601 G V I D L I F E K A I S E P N F S V A Y A N M C R C L M A L GI 2660712

5/15

FIGURE 2D

819	KVPMA	DKPGNT	VNFRK	LLLNRC	QKFF	EKDK	1252206
631	KVP	TEKPT	VNFRK	LLLNRC	QKFF	EKDK	GI 2660712
849	ADD	VFEKK	QKELE	ASAP	EERT	RLHDELE	1252206
661	DD	EFVFEKK	QKEMDE	ATA	EERGR	LKEELE	GI 2660712
879	EAK	DKARRRS	IGNIK	FIGEL	FKL	KMLTEAI	1252206
691	EARD	IARRRS	LGNIK	FIGEL	FKL	KMLTEAI	GI 2660712
909	MHDC	VVKLL	KNHDE	ESLE	CLCR	LLTTIGKD	1252206
721	MHDC	VVKLL	KNHDE	ESLE	CLCR	LLTTIGKD	GI 2660712
939	LDFE	KAKPR	MDQY	FNQME	KIVK	EKKTSRI	1252206
751	LDFE	KAKPR	MDQY	FNQME	KIK	EKKTSRI	GI 2660712
969	RFML	QDDV	IDLRL	CNWS	RRA	DQGP	1252206
781	RFML	QDDV	IDLRL	CNWS	VR	GDQGP	GI 2660712
999	HKEA	KIEEQ	EEQR	KVQQ	LMTK	- -	1252206
811	HKEA	EMEER	EH	IKVQQ	LM	AKGSD	GI 2660712

6/15

FIGURE 2E

7/15

1024	- - P G V Q R - - - -	V D E G G W N T V Q G A K N S R V L D	1252206
841	P G P I S R G L P L V D D G G W N T V P I S K G S R P I D	GI 2660712	
1048	P S K F L K I T K P -	T I D E K I Q L V P K A Q L G S W G K	1252206
871	T S R L T K I T K P G S I D S N N Q L F A P G G R L S W G K	GI 2660712	
1077	G S S G G - - A K A S E T - -	D A L R S S A S S L N R F S A	1252206
901	G S S G G S G A K P S D A A S E A A R P A T S T L N R F S A	GI 2660712	
1103	L Q P P A P S G S T P S T P V E F D S R R T L T S R G S M G	1252206	
931	L Q Q A V P T E S T - - - - -	D N R R V V Q - R S S L S	GI 2660712
1133	R E K N D K P L P S A T A R P N T F M R G G S S K D L L D N	1252206	
953	R E R G E K A - G D R G D R L E R S E R G G D R G D R L D R	GI 2660712	
1163	Q S Q E E Q R R - - - -	E M L E T V K Q L T G G V D V E R N	1252206
982	A R T P A T K R S F S K E V E E R S R E R P S Q P E G L R K	GI 2660712	
1189	S T E - - A E R N K T R E S A K P E I S A M S A H D -	K A A	1252206
1012	A A S L T E D R D R G R D A V K R E A A L P P V S P L K A A	GI 2660712	

FIGURE 2F

1216 L S E E E L E R K S K S I I D E F L H I N D F K E A M Q C V 1252206
 1042 L S E E E L E K K S K A I I E E Y L H L N D M K E A V Q C V GI 2660712

 1246 E E L N A Q G L L H V F V R V G V E S T L E R S Q I T R D H 1252206
 1072 Q E L A S P S L L F I F V R H G V E S T L E R S A I A R E H GI 2660712

 1276 M G Q L L Y Q L V Q S E K L S K Q D F F K G F S E T L E L A 1252206
 1102 M G Q L L H Q L L C A G H L S T A Q Y Y Q G L Y E I L E L A GI 2660712

 1306 D D M A I D I P H I W L Y L A E L V T P M L K E G G I S M R 1252206
 1132 E D M E I D I P H V W L Y L A E L V T P I L Q E G G V P M G GI 2660712

 1336 E L T I E F S K P L L P V G R A G V L L S E I L H L L C K Q 1252206
 1162 E L F R E I T K P L R P L G K A A S L L L E I L G L L C K S GI 2660712

 1366 M S H K K V G A L W R E A D L S W K D F L P E G E D V H N F 1252206
 1192 M G P K K V G T L W R E A G L S W K E F L P E G Q D I G A F GI 2660712

 1396 L L E Q K L D F I E S D S P C S S E A L S K K E L S A E E L 1252206
 1222 V A E Q K V E Y T L G E - - - E S E A P G Q R A L P S E E L GI 2660712

8/15

FIGURE 2G

9/15

1426	Y K R L E K L I I E D K A N D E Q I F D W V E A N L D E I Q	1252206
1249	N R Q L E K L L K E G - S S N Q R V F D W I E A N L S E Q Q	GI 2660712
1456	M S S P T F L R A L M T A V C K A A I I A D S S T F R V D T	1252206
1278	I V S N T L V R A L M T A V C Y S A I I F E T P - L R V D V	GI 2660712
1486	A V I K Q R V P I L L K Y L D S D T E K E L Q A L Y A L Q A	1252206
1307	A V L K A R A K L L Q K Y L - C D E Q K E L Q A L Y A L Q A	GI 2660712
1516	S I V K L D Q P A N L L R M F F D C L Y D E E V I S E D A F	1252206
1336	L V V T L E Q P P N L L R M F F D A L Y D E D V V K E D A F	GI 2660712
1546	Y K W E S S K D P A E Q N G K G V A L K S V T A F F T W L R	1252206
1366	Y S W E S S K D P A E Q Q G K G V A L K S V T A F F K W L R	GI 2660712
1576	E A E E E S E D N	1252206
1396	E A E E E S D H N	GI 2660712

FIGURE 2H

10/15

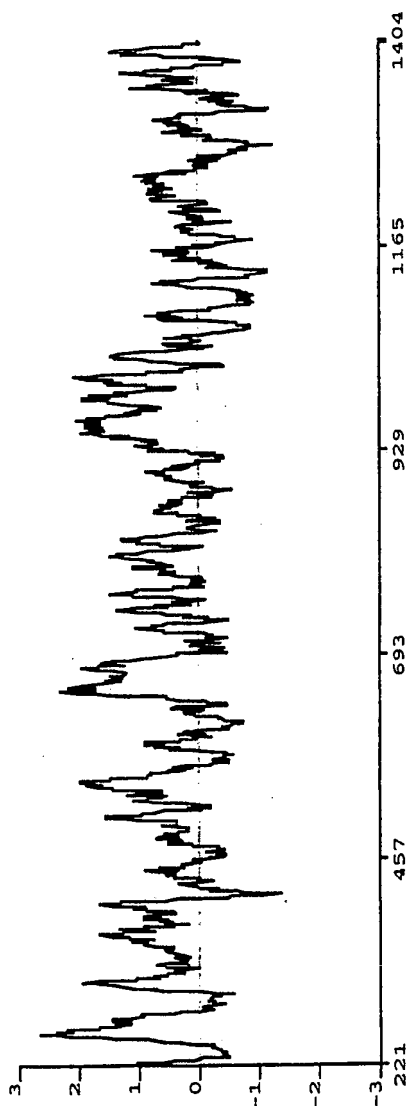


FIGURE 3A

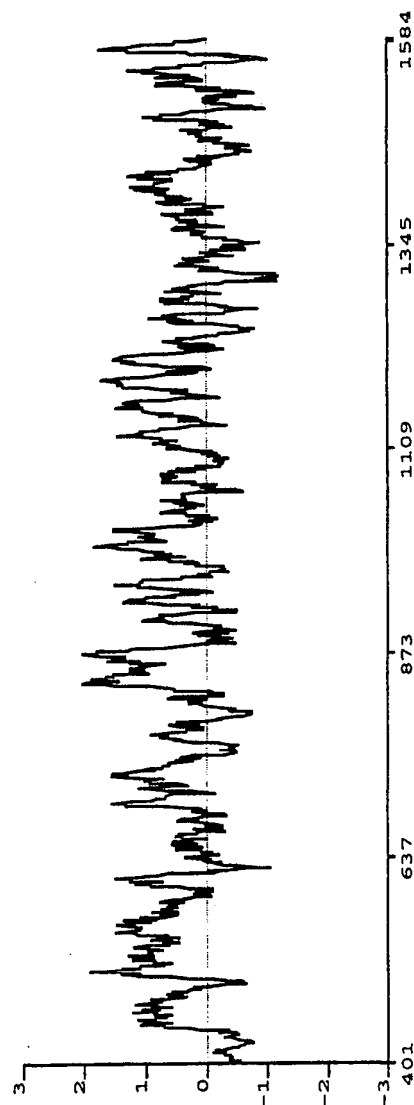


FIGURE 3B

11/15

[illegible]

FIGURE 4A

12/15

15	L	L	E	E	F	L	S	L	Q	M	E	I	L	T	E	L	G	L	H	F	R	V	L	D	M	P	T	Q	E	L	2950994	
181	E	L	E	E	F	F	K	N	I	E	V	D	L	F	R	R	L	G	L	N	F	R	L	L	D	M	P	P	C	E	L	GI 2440051
45	G	L	P	A	Y	R	K	F	D	I	E	A	W	M	P	G	R	G	R	F	G	E	V	T	S	A	S	N	C	T	2950994	
211	G	A	P	A	Y	Q	K	Y	D	I	E	A	W	M	P	G	R	Q	M	W	G	E	I	S	S	C	S	N	C	T	GI 2440051	
75	D	F	Q	S	R	R	L	H	I	M	F	Q	T	E	A	-	G	E	L	Q	F	A	H	T	V	N	A	T	A	C	2950994	
241	D	Y	Q	A	R	R	L	G	I	R	Y	R	R	S	A	D	G	Q	I	L	H	A	H	T	I	N	G	T	A	T	GI 2440051	
104	A	V	P	R	L	L	I	A	L	E	S	N	Q	Q	K	D	G	S	V	L	V	P	P	A	L	Q	S	Y	L	2950994		
271	A	I	P	R	L	L	I	A	L	E	S	Y	Q	-	K	E	D	G	I	E	I	P	A	V	L	R	P	F	M	GI 2440051		
134	G	T	D	R	-	I	T	A	P	T	H	V	P	-	-	-	-	L	Q	Y	I	G	P	N	Q	P	R	K	P	G	2950994	
300	D	N	Q	E	L	I	T	R	N	K	R	I	P	E	T	K	L	V	K	F	I	K	A							GI 2440051		
159	L	P	G	Q	P	A	V	S																					2950994			
322																													GI 2440051			

FIGURE 4B

13/15

FIGURE 5A

14/15

181	E D L Q K M K Q F A Q D F V M H T D V R T C S S S T S V I A	3461657
25	- - - - -	GI 1808648
211	D L Q E D E D G V Y F S S Y G H Y G I H E E M L K D K I R T	3461657
25	- - - - - Y F D S Y A H F G I H E E M L K D E V R T	GI 1808648
241	E S Y R D F I Y Q N P H I F K D K V V L D V G C G T G I L S	3461657
46	L T Y R N S M F H N R H L F K D K V V L D V G S G T G I L C	GI 1808648
271	M F A A K A G A K K V L G V D Q S E I L Y Q A M D I I R L N	3461657
76	M F A A K A G A R K V I G I V C S S I S D Y A V K I V K A N	GI 1808648
301	K L E D T I T L I K G K I E E V H L P V E K V D V I I S E W	3461657
106	K L D H V V T I I K G K V E E V E L P V E K V D I I I S E W	GI 1808648
331	M G Y F L L F E S M L D S V L Y A K N K Y L A K G G S V Y P	3461657
136	M G Y C L F Y E S M L N T V L Y A R D K W L A P D G L I F P	GI 1808648

FIGURE 5B

15/15

361	D	I	C	T	I	S	L	V	A	V	S	D	V	N	K	H	A	D	R	I	A	F	W	D	D	V	Y	G	F	K	3461657
166	D	R	A	T	L	Y	V	T	A	I	E	D	R	Q	Y	K	D	Y	K	I	H	W	E	N	V	Y	G	F	D	GI 1808648	
391	M	S	C	M	K	K	A	V	I	P	E	A	V	E	V	L	D	P	K	T	L	I	S	E	P	C	G	I	K	3461657	
196	M	S	C	I	K	D	V	A	I	K	E	P	L	V	D	V	D	P	K	Q	L	V	T	N	A	C	L	I	K	GI 1808648	
421	H	I	D	C	H	T	T	S	I	S	D	L	E	F	S	S	D	F	T	L	K	I	T	R	T	S	M	C	T	A	3461657
226	E	V	D	I	Y	T	V	K	V	E	D	L	T	F	T	S	P	F	C	L	Q	V	K	R	N	D	Y	V	H	A	GI 1808648
451	I	A	G	Y	F	D	I	Y	F	E	K	N	C	H	N	R	V	F	S	T	G	P	Q	S	T	K	T	H	W	3461657	
256	L	V	A	Y	F	N	I	E	F	T	R	-	C	H	K	R	T	G	F	S	T	S	P	E	S	P	Y	T	H	W	GI 1808648
481	K	Q	T	V	F	L	L	E	K	P	F	S	V	K	A	G	E	A	L	K	G	K	V	T	V	H	K	N	K	K	3461657
285	K	Q	T	V	F	Y	M	E	D	Y	L	T	V	K	T	G	E	E	I	F	G	T	I	G	M	R	P	N	A	K	GI 1808648
511	D	P	R	S	L	T	V	T	L	T	L	N	-	-	-	-	-	-	-	-	N	S	T	Q	T	Y	G	L	Q	3461657	
315	N	N	R	D	L	D	F	T	I	D	L	D	F	K	G	Q	L	C	E	L	S	C	S	T	D	Y	R	M	R	GI 1808648	

FIGURE 5C

SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.

TANG, Y. Tom
 CORLEY, Neil C.
 GUEGLER, Karl J.
 GORGONE, Gina A.
 PATTERSON, Chandra
 HILLMAN, Jennifer L.
 BAUGHN, Mariah R.
 LAL, Preeti
 AZIMZAI, Yalda
 YUE, Henry
 YANG, Junming

<120> RNA-ASSOCIATED PROTEINS

<130> PF-0600 PCT

<140> To Be Assigned

<141> Herewith

<150> 09/156,039; unassigned; 09/158,720; unassigned; 09/186,815;
 unassigned; 60/128,660

<151> 1998-09-17; 1998-09-17; 1998-09-22; 1998-09-22; 1998-11-04;
 1998-11-04; 1999-04-08

<160> 38

<170> PERL Program

<210> 1

<211> 216

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 399781CD1

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Asn	Val	Ala	Asp	Asp	Thr	Arg	Ser	Glu	Asp	Leu	Arg	Arg	Glu	Phe
			20						25					30
Gly	Arg	Tyr	Gly	Pro	Ile	Val	Asp	Val	Tyr	Val	Pro	Leu	Asp	Phe
			35						40					45
Tyr	Thr	Arg	Arg	Pro	Arg	Gly	Phe	Ala	Tyr	Val	Gln	Phe	Glu	Asp
			50						55					60
Val	Arg	Asp	Ala	Glu	Asp	Ala	Leu	His	Asn	Leu	Asp	Arg	Lys	Trp
			65						70					75
Ile	Cys	Gly	Arg	Gln	Ile	Glu	Ile	Gln	Phe	Ala	Gln	Gly	Asp	Arg
			80						85					90
Lys	Thr	Pro	Asn	Gln	Met	Lys	Ala	Lys	Glu	Gly	Arg	Asn	Val	Tyr
			95						100					105
Ser	Ser	Ser	Arg	Tyr	Asp	Asp	Tyr	Asp	Arg	Tyr	Arg	Arg	Ser	Arg
			110						115					120

Ser	Arg	Ser	Tyr	Glu	Arg	Arg	Arg	Ser	Arg	Ser	Arg	Ser	Phe	Asp
				125					130					135
Tyr	Asn	Tyr	Arg	Arg	Ser	Tyr	Ser	Pro	Arg	Asn	Ser	Arg	Pro	Thr
				140					145					150
Gly	Arg	Pro	Arg	Arg	Arg	Glu	Ala	Ile	Pro	Thr	Met	Ile	Asp	Gln
				155					160					165
Thr	Ala	Ala	Gly	Ile	Pro	Ser	Thr	Val	Leu	Leu	Thr	Thr	Leu	Gln
				170					175					180
Glu	Arg	Ser	Glu	Ser	Gly	Lys	Arg	Thr	Lys	Glu	Gly	Gln	Phe	Lys
				185					190					195
Arg	Pro	Lys	Gly	Gly	Trp	Lys	Val	Leu	Gln	Tyr	Glu	Tyr	Cys	Thr
				200					205					210
Asn	Ile	Leu	Thr	Leu	Val									
				215										

<210> 2

<211> 1584

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 1252206CD1

<400> 2

Met	Asn	Ser	Gln	Pro	Gln	Thr	Arg	Ser	Pro	Phe	Phe	Gln	Arg	Pro
1				5					10					15
Gln	Ile	Gln	Pro	Pro	Arg	Ala	Thr	Ile	Pro	Asn	Ser	Ser	Pro	Ser
				20					25					30
Ile	Arg	Pro	Gly	Ala	Gln	Thr	Pro	Thr	Ala	Val	Tyr	Gln	Ala	Asn
				35					40					45
Gln	His	Ile	Met	Met	Val	Asn	His	Leu	Pro	Met	Pro	Tyr	Pro	Val
				50					55					60
Pro	Gln	Gly	Pro	Gln	Tyr	Cys	Ile	Pro	Gln	Tyr	Arg	His	Ser	Gly
				65					70					75
Pro	Pro	Tyr	Val	Gly	Pro	Pro	Gln	Lys	Tyr	Pro	Val	Gln	Pro	Pro
				80					85					90
Gly	Pro	Gly	Pro	Phe	Tyr	Pro	Gly	Pro	Gly	Pro	Gly	Asp	Phe	Pro
				95					100					105
Asn	Ala	Tyr	Gly	Thr	Pro	Phe	Tyr	Pro	Ser	Gln	Pro	Val	Tyr	Gln
				110					115					120
Ser	Ala	Pro	Ile	Ile	Val	Pro	Thr	Gln	Gln	Gln	Pro	Pro	Pro	Ala
				125					130					135
Lys	Arg	Glu	Lys	Lys	Thr	Ile	Arg	Ile	Arg	Asp	Pro	Asn	Gln	Gly
				140					145					150
Gly	Lys	Asp	Ile	Thr	Glu	Glu	Ile	Met	Ser	Gly	Gly	Gly	Ser	Arg
				155					160					165
Asn	Pro	Thr	Pro	Pro	Ile	Gly	Arg	Pro	Thr	Ser	Thr	Pro	Thr	Pro
				170					175					180
Pro	Gln	Leu	Pro	Ser	Gln	Val	Pro	Glu	His	Ser	Pro	Val	Val	Tyr
				185					190					195
Gly	Thr	Val	Glu	Ser	Ala	His	Leu	Ala	Ala	Ser	Thr	Pro	Val	Thr
				200					205					210
Ala	Ala	Ser	Asp	Gln	Lys	Gln	Glu	Glu	Lys	Pro	Lys	Pro	Asp	Pro
				215					220					225
Val	Leu	Lys	Ser	Pro	Ser	Pro	Val	Leu	Arg	Leu	Val	Leu	Ser	Gly

	230		235		240
Glu Lys Lys Glu	Gln Glu Gly Gln Thr	Ser Glu Thr Thr Ala	Ile		
	245		250		255
Val Ser Ile Ala	Glu Leu Pro Leu Pro	Pro Ser Pro Thr Thr	Val		
	260		265		270
Ser Ser Val Ala	Arg Ser Thr Ile Ala	Ala Pro Thr Ser Ser	Ala		
	275		280		285
Leu Ser Ser Gln	Pro Ile Phe Thr Thr	Ala Ile Asp Asp Arg	Cys		
	290		295		300
Glu Leu Ser Ser	Pro Arg Glu Asp Thr	Ile Pro Ile Pro Ser	Leu		
	305		310		315
Thr Ser Cys Thr	Glu Thr Ser Asp Pro	Leu Pro Thr Asn Glu	Asn		
	320		325		330
Asp Asp Asp Ile	Cys Lys Lys Pro Cys	Ser Val Ala Pro Asn	Asp		
	335		340		345
Ile Pro Leu Val	Ser Ser Thr Asn Leu	Ile Asn Glu Ile Asn	Gly		
	350		355		360
Val Ser Glu Lys	Leu Ser Ala Thr Glu	Ser Ile Val Glu Ile	Val		
	365		370		375
Lys Gln Glu Val	Leu Pro Leu Thr Leu	Glu Leu Glu Ile Leu	Glu		
	380		385		390
Asn Pro Pro Glu	Glu Met Lys Leu Glu	Cys Ile Pro Ala Pro	Ile		
	395		400		405
Thr Pro Ser Thr	Val Pro Ser Phe Pro	Pro Thr Pro Pro Thr	Pro		
	410		415		420
Pro Ala Ser Pro	Pro His Thr Pro Val	Ile Val Pro Ala Ala	Ala		
	425		430		435
Thr Thr Val Ser	Ser Pro Ser Ala Ala	Ile Thr Val Gln Arg	Val		
	440		445		450
Leu Glu Glu Asp	Glu Ser Ile Arg Thr	Cys Leu Ser Glu Asp	Ala		
	455		460		465
Lys Glu Ile Gln	Asn Lys Ile Glu Val	Glu Ala Asp Gly Gln	Thr		
	470		475		480
Glu Glu Ile Leu	Asp Ser Gln Asn Leu	Asn Ser Arg Arg Ser	Pro		
	485		490		495
Val Pro Ala Gln	Ile Ala Ile Thr Val	Pro Lys Thr Trp Lys	Lys		
	500		505		510
Pro Lys Asp Arg	Thr Arg Thr Thr Glu	Glu Met Leu Glu Ala	Glu		
	515		520		525
Leu Glu Leu Lys	Ala Glu Glu Glu Leu	Ser Ile Asp Lys Val	Leu		
	530		535		540
Glu Ser Glu Gln	Asp Lys Met Ser Gln	Gly Phe His Pro Glu	Arg		
	545		550		555
Asp Pro Ser Asp	Leu Lys Lys Val Lys	Ala Val Glu Glu Asn	Gly		
	560		565		570
Glu Glu Ala Glu	Pro Val Arg Asn Gly	Ala Glu Ser Val Ser	Glu		
	575		580		585
Gly Glu Gly Ile	Asp Ala Asn Ser Gly	Ser Thr Asp Ser Ser	Gly		
	590		595		600
Asp Gly Val Thr	Phe Pro Phe Lys Pro	Glu Ser Trp Lys Pro	Thr		
	605		610		615
Asp Thr Glu Gly	Lys Lys Gln Tyr Asp	Arg Glu Phe Leu Leu	Asp		
	620		625		630
Phe Gln Phe Met	Pro Ala Cys Ile Gln	Lys Pro Glu Gly Leu	Pro		
	635		640		645
Pro Ile Ser Asp	Val Val Leu Asp Lys	Ile Asn Gln Pro Lys	Leu		
	650		655		660

Pro Met Arg Thr	Leu Asp Pro Arg Ile	Leu Pro Arg Gly Pro Asp	665	670	675
Phe Thr Pro Ala	Phe Ala Asp Phe Gly Arg	Gln Thr Pro Gly Gly	680	685	690
Arg Gly Val Pro	Leu Leu Asn Val Gly Ser	Arg Arg Ser Gln Pro	695	700	705
Gly Gln Arg Arg	Glu Pro Arg Lys Ile Ile	Thr Val Ser Val Lys	710	715	720
Glu Asp Val His	Leu Lys Lys Ala Glu Asn	Ala Trp Lys Pro Ser	725	730	735
Gln Lys Arg Asp	Ser Gln Ala Asp Asp Pro	Glu Asn Ile Lys Thr	740	745	750
Gln Glu Leu Phe	Arg Lys Val Arg Ser Ile	Leu Asn Lys Leu Thr	755	760	765
Pro Gln Met Phe	Asn Gln Leu Met Lys Gln	Val Ser Gly Leu Thr	770	775	780
Val Asp Thr Glu	Glu Arg Leu Lys Gly Val	Ile Asp Leu Val Phe	785	790	795
Glu Lys Ala Ile	Asp Glu Pro Ser Phe Ser	Val Ala Tyr Ala Asn	800	805	810
Met Cys Arg Cys	Leu Val Thr Leu Lys Val	Pro Met Ala Asp Lys	815	820	825
Pro Gly Asn Thr	Val Asn Phe Arg Lys Leu	Leu Leu Asn Arg Cys	830	835	840
Gln Lys Glu Phe	Glu Lys Asp Lys Ala Asp	Asp Asp Val Phe Glu	845	850	855
Lys Lys Gln Lys	Glu Leu Glu Ala Ala Ser	Ala Pro Glu Glu Arg	860	865	870
Thr Arg Leu His	Asp Glu Leu Glu Glu Ala	Lys Asp Lys Ala Arg	875	880	885
Arg Arg Ser Ile	Gly Asn Ile Lys Phe Ile	Gly Glu Leu Phe Lys	890	895	900
Leu Lys Met Leu	Thr Glu Ala Ile Met His	Asp Cys Val Val Lys	905	910	915
Leu Leu Lys Asn	His Asp Glu Glu Ser Leu	Glu Cys Leu Cys Arg	920	925	930
Leu Leu Thr Thr	Ile Gly Lys Asp Leu Asp	Phe Glu Lys Ala Lys	935	940	945
Pro Arg Met Asp	Gln Tyr Phe Asn Gln Met	Glu Lys Ile Val Lys	950	955	960
Glu Lys Lys Thr	Ser Ser Arg Ile Arg Phe	Met Leu Gln Asp Val	965	970	975
Ile Asp Leu Arg	Leu Cys Asn Trp Val Ser	Arg Arg Ala Asp Gln	980	985	990
Gly Pro Lys Thr	Ile Glu Gln Ile His Lys	Glu Ala Lys Ile Glu	995	1000	1005
Glu Gln Glu Glu	Gln Arg Lys Val Gln Gln	Leu Met Thr Lys Glu	1010	1015	1020
Lys Arg Arg Pro	Gly Val Gln Arg Val Asp	Glu Gly Gly Trp Asn	1025	1030	1035
Thr Val Gln Gly	Ala Lys Asn Ser Arg Val	Leu Asp Pro Ser Lys	1040	1045	1050
Phe Leu Lys Ile	Thr Lys Pro Thr Ile Asp	Glu Lys Ile Gln Leu	1055	1060	1065
Val Pro Lys Ala	Gln Leu Gly Ser Trp Gly	Lys Gly Ser Ser Gly	1070	1075	1080
Gly Ala Lys Ala	Ser Glu Thr Asp Ala Leu	Arg Ser Ser Ala Ser			

1085	1090	1095
Ser Leu Asn Arg Phe	Ser Ala Leu Gln Pro	Pro Ala Pro Ser Gly
1100	1105	1110
Ser Thr Pro Ser Thr	Pro Val Glu Phe Asp	Ser Arg Arg Thr Leu
1115	1120	1125
Thr Ser Arg Gly Ser	Met Gly Arg Glu Lys	Asn Asp Lys Pro Leu
1130	1135	1140
Pro Ser Ala Thr Ala	Arg Pro Asn Thr Phe	Met Arg Gly Gly Ser
1145	1150	1155
Ser Lys Asp Leu Leu	Asp Asn Gln Ser Gln	Glu Glu Gln Arg Arg
1160	1165	1170
Glu Met Leu Glu Thr	Val Lys Gln Leu Thr	Gly Gly Val Asp Val
1175	1180	1185
Glu Arg Asn Ser Thr	Glu Ala Glu Arg Asn	Lys Thr Arg Glu Ser
1190	1195	1200
Ala Lys Pro Glu Ile	Ser Ala Met Ser Ala	His Asp Lys Ala Ala
1205	1210	1215
Leu Ser Glu Glu Glu	Leu Glu Arg Lys Ser	Lys Ser Ile Ile Asp
1220	1225	1230
Glu Phe Leu His Ile	Asn Asp Phe Lys Glu	Ala Met Gln Cys Val
1235	1240	1245
Glu Glu Leu Asn Ala	Gln Gly Leu Leu His	Val Phe Val Arg Val
1250	1255	1260
Gly Val Glu Ser Thr	Leu Glu Arg Ser Gln	Ile Thr Arg Asp His
1265	1270	1275
Met Gly Gln Leu Leu	Tyr Gln Leu Val Gln	Ser Glu Lys Leu Ser
1280	1285	1290
Lys Gln Asp Phe Phe	Lys Gly Phe Ser Glu	Thr Leu Glu Leu Ala
1295	1300	1305
Asp Asp Met Ala Ile	Asp Ile Pro His Ile	Trp Leu Tyr Leu Ala
1310	1315	1320
Glu Leu Val Thr Pro	Met Leu Lys Glu Gly	Gly Ile Ser Met Arg
1325	1330	1335
Glu Leu Thr Ile Glu	Phe Ser Lys Pro Leu	Leu Pro Val Gly Arg
1340	1345	1350
Ala Gly Val Leu Leu	Ser Glu Ile Leu His	Leu Leu Cys Lys Gln
1355	1360	1365
Met Ser His Lys Lys	Val Gly Ala Leu Trp	Arg Glu Ala Asp Leu
1370	1375	1380
Ser Trp Lys Asp Phe	Leu Pro Glu Gly Glu	Asp Val His Asn Phe
1385	1390	1395
Leu Leu Glu Gln Lys	Leu Asp Phe Ile Glu	Ser Asp Ser Pro Cys
1400	1405	1410
Ser Ser Glu Ala Leu	Ser Lys Lys Glu Leu	Ser Ala Glu Glu Leu
1415	1420	1425
Tyr Lys Arg Leu Glu	Lys Leu Ile Ile Glu	Asp Lys Ala Asn Asp
1430	1435	1440
Glu Gln Ile Phe Asp	Trp Val Glu Ala Asn	Leu Asp Glu Ile Gln
1445	1450	1455
Met Ser Ser Pro Thr	Phe Leu Arg Ala Leu	Met Thr Ala Val Cys
1460	1465	1470
Lys Ala Ala Ile Ile	Ala Asp Ser Ser Thr	Phe Arg Val Asp Thr
1475	1480	1485
Ala Val Ile Lys Gln	Arg Val Pro Ile Leu	Leu Lys Tyr Leu Asp
1490	1495	1500
Ser Asp Thr Glu Lys	Glu Leu Gln Ala Leu	Tyr Ala Leu Gln Ala
1505	1510	1515

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Ser Ile Val Lys Leu Asp Gln Pro Ala Asn Leu Leu Arg Met Phe
      1520                      1525                      1530
Phe Asp Cys Leu Tyr Asp Glu Glu Val Ile Ser Glu Asp Ala Phe
      1535                      1540                      1545
Tyr Lys Trp Glu Ser Ser Lys Asp Pro Ala Glu Gln Asn Gly Lys
      1550                      1555                      1560
Gly Val Ala Leu Lys Ser Val Thr Ala Phe Phe Thr Trp Leu Arg
      1565                      1570                      1575
Glu Ala Glu Glu Glu Ser Glu Asp Asn
      1580

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<210> 3
<211> 166
<212> PRT
<213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte ID No.: 2950994CD1

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<400> 3
Met Phe Gly Val Thr Gly Pro Gly Leu Glu Gln Ser Ser Gln Leu
  1           5           10           15
Leu Glu Glu Phe Leu Ser Leu Gln Met Glu Ile Leu Thr Glu Leu
      20           25           30
Gly Leu His Phe Arg Val Leu Asp Met Pro Thr Gln Glu Leu Gly
      35           40           45
Leu Pro Ala Tyr Arg Lys Phe Asp Ile Glu Ala Trp Met Pro Gly
      50           55           60
Arg Gly Arg Phe Gly Glu Val Thr Ser Ala Ser Asn Cys Thr Asp
      65           70           75
Phe Gln Ser Arg Arg Leu His Ile Met Phe Gln Thr Glu Ala Gly
      80           85           90
Glu Leu Gln Phe Ala His Thr Val Asn Ala Thr Ala Cys Ala Val
      95           100          105
Pro Arg Leu Leu Ile Ala Leu Leu Glu Ser Asn Gln Gln Lys Asp
      110          115          120
Gly Ser Val Leu Val Pro Pro Ala Leu Gln Ser Tyr Leu Gly Thr
      125          130          135
Asp Arg Ile Thr Ala Pro Thr His Val Pro Leu Gln Tyr Ile Gly
      140          145          150
Pro Asn Gln Pro Arg Lys Pro Gly Leu Pro Gly Gln Pro Ala Val
      155          160          165
Ser

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<210> 4
<211> 531
<212> PRT
<213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte ID No.: 3461657CD1

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<400> 4

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Met	Cys	Ser	Leu	Ala	Ser	Gly	Ala	Thr	Gly	Gly	Arg	Gly	Ala	Val	1	5	10	15
Glu	Asn	Glu	Glu	Asp	Leu	Pro	Glu	Leu	Ser	Asp	Ser	Gly	Asp	Glu	20	25	30	
Ala	Ala	Trp	Glu	Asp	Glu	Asp	Asp	Ala	Asp	Leu	Pro	His	Gly	Lys	35	40	45	
Gln	Gln	Thr	Pro	Cys	Leu	Phe	Cys	Asn	Arg	Leu	Phe	Thr	Ser	Ala	50	55	60	
Glu	Glu	Thr	Phe	Ser	His	Cys	Lys	Ser	Glu	His	Gln	Phe	Asn	Ile	65	70	75	
Asp	Ser	Met	Val	His	Lys	His	Gly	Leu	Glu	Phe	Tyr	Gly	Tyr	Ile	80	85	90	
Lys	Leu	Ile	Asn	Phe	Ile	Arg	Leu	Lys	Asn	Pro	Thr	Val	Glu	Tyr	95	100	105	
Met	Asn	Ser	Ile	Tyr	Asn	Pro	Val	Pro	Trp	Glu	Lys	Glu	Glu	Tyr	110	115	120	
Leu	Lys	Pro	Val	Leu	Glu	Asp	Asp	Leu	Leu	Leu	Gln	Phe	Asp	Val	125	130	135	
Glu	Asp	Leu	Tyr	Glu	Pro	Val	Ser	Val	Pro	Phe	Ser	Tyr	Pro	Asn	140	145	150	
Gly	Leu	Ser	Glu	Asn	Thr	Ser	Val	Val	Glu	Lys	Leu	Lys	His	Met	155	160	165	
Glu	Ala	Arg	Ala	Leu	Ser	Ala	Glu	Ala	Ala	Leu	Ala	Arg	Ala	Arg	170	175	180	
Glu	Asp	Leu	Gln	Lys	Met	Lys	Gln	Phe	Ala	Gln	Asp	Phe	Val	Met	185	190	195	
His	Thr	Asp	Val	Arg	Thr	Cys	Ser	Ser	Ser	Thr	Ser	Val	Ile	Ala	200	205	210	
Asp	Leu	Gln	Glu	Asp	Glu	Asp	Gly	Val	Tyr	Phe	Ser	Ser	Tyr	Gly	215	220	225	
His	Tyr	Gly	Ile	His	Glu	Glu	Met	Leu	Lys	Asp	Lys	Ile	Arg	Thr	230	235	240	
Glu	Ser	Tyr	Arg	Asp	Phe	Ile	Tyr	Gln	Asn	Pro	His	Ile	Phe	Lys	245	250	255	
Asp	Lys	Val	Val	Leu	Asp	Val	Gly	Cys	Gly	Thr	Gly	Ile	Leu	Ser	260	265	270	
Met	Phe	Ala	Ala	Lys	Ala	Gly	Ala	Lys	Lys	Val	Leu	Gly	Val	Asp	275	280	285	
Gln	Ser	Glu	Ile	Leu	Tyr	Gln	Ala	Met	Asp	Ile	Ile	Arg	Leu	Asn	290	295	300	
Lys	Leu	Glu	Asp	Thr	Ile	Thr	Leu	Ile	Lys	Gly	Lys	Ile	Glu	Glu	305	310	315	
Val	His	Leu	Pro	Val	Glu	Lys	Val	Asp	Val	Ile	Ile	Ser	Glu	Trp	320	325	330	
Met	Gly	Tyr	Phe	Leu	Leu	Phe	Glu	Ser	Met	Leu	Asp	Ser	Val	Leu	335	340	345	
Tyr	Ala	Lys	Asn	Lys	Tyr	Leu	Ala	Lys	Gly	Gly	Ser	Val	Tyr	Pro	350	355	360	
Asp	Ile	Cys	Thr	Ile	Ser	Leu	Val	Ala	Val	Ser	Asp	Val	Asn	Lys	365	370	375	
His	Ala	Asp	Arg	Ile	Ala	Phe	Trp	Asp	Asp	Val	Tyr	Gly	Phe	Lys	380	385	390	
Met	Ser	Cys	Met	Lys	Lys	Ala	Val	Ile	Pro	Glu	Ala	Val	Val	Glu	395	400	405	
Val	Leu	Asp	Pro	Lys	Thr	Leu	Ile	Ser	Glu	Pro	Cys	Gly	Ile	Lys	410	415	420	
His	Ile	Asp	Cys	His	Thr	Thr	Ser	Ile	Ser	Asp	Leu	Glu	Phe	Ser				

	425	430	435
Ser Asp Phe Thr	Leu Lys Ile Thr Arg Thr	Ser Met Cys Thr	Ala
	440	445	450
Ile Ala Gly Tyr	Phe Asp Ile Tyr Phe Glu	Lys Asn Cys His	Asn
	455	460	465
Arg Val Val Phe	Ser Thr Gly Pro Gln Ser	Thr Lys Thr His	Trp
	470	475	480
Lys Gln Thr Val	Phe Leu Leu Glu Lys Pro	Phe Ser Val Lys	Ala
	485	490	495
Gly Glu Ala Leu	Lys Gly Lys Val Thr Val	His Lys Asn Lys	Lys
	500	505	510
Asp Pro Arg Ser	Leu Thr Val Thr Leu Thr	Leu Asn Asn Ser	Thr
	515	520	525
Gln Thr Tyr Gly	Leu Gln		
	530		

<210> 5
 <211> 148
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No.: 053076CD1

<400> 5	
Met Ala Ser Val Val	Leu Ala Leu Arg Thr Arg Thr Ala Val Thr
1	5 10 15
Ser Leu Leu Ser Pro	Thr Pro Ala Thr Ala Leu Ala Val Arg Tyr
	20 25 30
Ala Ser Lys Lys Ser	Gly Gly Ser Ser Lys Asn Leu Gly Gly Lys
	35 40 45
Ser Ser Gly Arg Arg	Gln Gly Ile Lys Lys Met Glu Gly His Tyr
	50 55 60
Val His Ala Gly Asn	Ile Ile Ala Thr Gln Arg His Phe Arg Trp
	65 70 75
His Pro Gly Ala His	Val Gly Val Gly Lys Asn Lys Cys Leu Tyr
	80 85 90
Ala Leu Glu Glu Gly	Ile Val Arg Tyr Thr Lys Glu Val Tyr Val
	95 100 105
Pro His Pro Arg Asn	Thr Glu Ala Val Asp Leu Ile Thr Arg Leu
	110 115 120
Pro Lys Gly Ala Val	Leu Tyr Lys Thr Phe Val His Val Val Pro
	125 130 135
Ala Lys Pro Glu Gly	Thr Phe Lys Leu Val Ala Met Leu
	140 145

<210> 6
 <211> 317
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No.: 1292379CD1

<400> 6

Met	Met	Ser	Phe	His	Ser	Asn	Arg	Pro	Ser	Lys	Arg	Phe	Cys	Ile
1				5					10					15
Phe	Lys	Lys	His	Ser	Glu	Asn	Leu	Arg	Gly	Ile	Thr	Leu	Val	Cys
				20					25					30
Leu	Asn	Cys	Asp	Phe	Leu	Ser	Asp	Val	Ser	Gly	Leu	Asp	Asn	Met
				35					40					45
Ala	Thr	His	Leu	Ser	Gln	His	Lys	Thr	His	Thr	Cys	Gln	Val	Val
				50					55					60
Met	Gln	Lys	Val	Ser	Val	Cys	Ile	Pro	Thr	Ser	Glu	His	Leu	Ser
				65					70					75
Glu	Leu	Lys	Lys	Glu	Ala	Pro	Ala	Lys	Glu	Gln	Glu	Pro	Val	Ser
				80					85					90
Lys	Glu	Ile	Ala	Arg	Pro	Asn	Met	Ala	Glu	Arg	Glu	Thr	Glu	Thr
				95					100					105
Ser	Asn	Ser	Glu	Ser	Lys	Gln	Asp	Lys	Ala	Ala	Ser	Ser	Lys	Glu
				110					115					120
Lys	Asn	Gly	Cys	Asn	Ala	Asn	Ser	Phe	Glu	Gly	Ser	Ser	Thr	Thr
				125					130					135
Lys	Ser	Glu	Glu	Ser	Ile	Thr	Val	Ser	Asp	Lys	Glu	Asn	Glu	Thr
				140					145					150
Cys	Leu	Ala	Asp	Gln	Glu	Thr	Gly	Ser	Lys	Asn	Ile	Val	Ser	Cys
				155					160					165
Asp	Ser	Asn	Ile	Gly	Ala	Asp	Lys	Val	Glu	Lys	Lys	Lys	Gln	Ile
				170					175					180
Gln	His	Val	Cys	Gln	Glu	Met	Glu	Leu	Lys	Met	Cys	Gln	Ser	Ser
				185					190					195
Glu	Asn	Ile	Ile	Leu	Ser	Asp	Gln	Ile	Lys	Asp	His	Asn	Ser	Ser
				200					205					210
Glu	Ala	Arg	Phe	Ser	Ser	Lys	Asn	Ile	Lys	Asp	Leu	Arg	Leu	Ala
				215					220					225
Ser	Asp	Asn	Val	Ser	Ile	Asp	Gln	Phe	Leu	Arg	Lys	Arg	His	Glu
				230					235					240
Pro	Glu	Ser	Val	Ser	Ser	Asp	Val	Ser	Glu	Gln	Gly	Ser	Ile	His
				245					250					255
Leu	Glu	Pro	Leu	Thr	Pro	Ser	Glu	Val	Leu	Glu	Tyr	Glu	Ala	Thr
				260					265					270
Glu	Ile	Leu	Gln	Lys	Gly	Ser	Gly	Asp	Pro	Ser	Ala	Lys	Thr	Asp
				275					280					285
Glu	Val	Val	Ser	Asp	Gln	Thr	Asp	Asp	Ile	Pro	Gly	Gly	Asn	Asn
				290					295					300
Pro	Ser	Thr	Thr	Glu	Ala	Thr	Val	Asp	Leu	Glu	Asp	Glu	Lys	Glu
				305					310					315

Arg Ser

<210> 7

<211> 278

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 1437783CD1

<400> 7

Met	Ala	Ala	Leu	Phe	Leu	Lys	Arg	Leu	Thr	Leu	Gln	Thr	Val	Lys
1			5						10					15
Ser	Glu	Asn	Ser	Cys	Ile	Arg	Cys	Phe	Gly	Lys	His	Ile	Leu	Gln
			20						25					30
Lys	Thr	Ala	Pro	Ala	Gln	Leu	Ser	Pro	Ile	Ala	Ser	Ala	Pro	Arg
			35						40					45
Leu	Ser	Phe	Leu	Ile	His	Ala	Lys	Ala	Phe	Ser	Thr	Ala	Glu	Asp
			50						55					60
Thr	Gln	Asn	Glu	Gly	Lys	Lys	Thr	Lys	Lys	Asn	Lys	Thr	Ala	Phe
			65						70					75
Ser	Asn	Val	Gly	Arg	Lys	Ile	Ser	Gln	Arg	Val	Ile	His	Leu	Phe
			80						85					90
Asp	Glu	Lys	Gly	Asn	Asp	Leu	Gly	Asn	Met	His	Arg	Ala	Asn	Val
			95						100					105
Ile	Arg	Leu	Met	Asp	Glu	Arg	Asp	Leu	Arg	Leu	Val	Gln	Arg	Asn
			110						115					120
Thr	Ser	Thr	Glu	Pro	Ala	Glu	Tyr	Gln	Leu	Met	Thr	Gly	Leu	Gln
			125						130					135
Ile	Leu	Gln	Glu	Arg	Gln	Arg	Leu	Arg	Glu	Met	Glu	Lys	Ala	Asn
			140						145					150
Pro	Lys	Thr	Gly	Pro	Thr	Leu	Arg	Lys	Glu	Leu	Ile	Leu	Ser	Ser
			155						160					165
Asn	Ile	Gly	Gln	His	Asp	Leu	Asp	Thr	Lys	Thr	Lys	Gln	Ile	Gln
			170						175					180
Gln	Trp	Ile	Lys	Lys	Lys	His	Leu	Val	Gln	Ile	Thr	Ile	Lys	Lys
			185						190					195
Gly	Lys	Asn	Val	Asp	Val	Ser	Glu	Asn	Glu	Met	Glu	Glu	Ile	Phe
			200						205					210
His	Gln	Ile	Leu	Gln	Thr	Met	Pro	Gly	Ile	Ala	Thr	Phe	Ser	Ser
			215						220					225
Arg	Pro	Gln	Ala	Val	Gln	Gly	Gly	Lys	Ala	Leu	Met	Cys	Val	Leu
			230						235					240
Arg	Ala	Leu	Ser	Lys	Asn	Glu	Glu	Lys	Ala	Tyr	Lys	Glu	Thr	Gln
			245						250					255
Glu	Thr	Gln	Glu	Arg	Asp	Thr	Leu	Asn	Lys	Asp	His	Gly	Asn	Asp
			260						265					270
Lys	Glu	Ser	Asn	Val	Leu	His	Gln							
			275											

<210> 8

<211> 586

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 1557635CD1

<400> 8

Met	Ser	Ala	Thr	Val	Val	Asp	Ala	Val	Asn	Ala	Ala	Pro	Leu	Ser
1				5					10					15
Gly	Ser	Lys	Glu	Met	Ser	Leu	Glu	Glu	Pro	Lys	Lys	Met	Thr	Arg
			20						25					30
Glu	Asp	Trp	Arg	Lys	Lys	Lys	Glu	Leu	Glu	Glu	Gln	Arg	Lys	Leu
			35						40					45

Gly Asn Ala Pro Ala Glu Val Asp Glu Glu Gly Lys Asp Ile Asn	50	55	60
Pro His Ile Pro Gln Tyr Ile Ser Ser Val Pro Trp Tyr Ile Asp	65	70	75
Pro Ser Lys Arg Pro Thr Leu Lys His Gln Arg Pro Gln Pro Glu	80	85	90
Lys Gln Lys Gln Phe Ser Ser Ser Gly Glu Trp Tyr Lys Arg Gly	95	100	105
Val Lys Glu Asn Ser Ile Ile Thr Lys Tyr Arg Lys Gly Ala Cys	110	115	120
Glu Asn Cys Gly Ala Met Thr His Lys Lys Lys Asp Cys Phe Glu	125	130	135
Arg Pro Arg Arg Val Gly Ala Lys Phe Thr Gly Thr Asn Ile Ala	140	145	150
Pro Asp Glu His Val Gln Pro Gln Leu Met Phe Asp Tyr Asp Gly	155	160	165
Lys Arg Asp Arg Trp Asn Gly Tyr Asn Pro Glu Glu His Met Lys	170	175	180
Ile Val Glu Glu Tyr Ala Lys Val Asp Leu Ala Lys Arg Thr Leu	185	190	195
Lys Ala Gln Lys Leu Gln Glu Glu Leu Ala Ser Gly Lys Leu Val	200	205	210
Glu Gln Ala Asn Ser Pro Lys His Gln Trp Gly Glu Glu Glu Pro	215	220	225
Asn Ser Gln Thr Glu Lys Asp His Asn Ser Glu Asp Glu Asp Glu	230	235	240
Asp Lys Tyr Ala Asp Asp Ile Asp Met Pro Gly Gln Asn Phe Asp	245	250	255
Ser Lys Arg Arg Ile Thr Val Arg Asn Leu Arg Ile Arg Glu Asp	260	265	270
Ile Ala Lys Tyr Leu Arg Asn Leu Asp Pro Asn Ser Ala Tyr Tyr	275	280	285
Asp Pro Lys Thr Arg Ala Met Arg Glu Asn Pro Tyr Ala Asn Ala	290	295	300
Gly Lys Asn Pro Asp Glu Val Ser Tyr Ala Gly Asp Asn Phe Val	305	310	315
Arg Tyr Thr Gly Asp Thr Ile Ser Met Ala Gln Thr Gln Leu Phe	320	325	330
Ala Trp Glu Ala Tyr Asp Lys Gly Ser Glu Val His Leu Gln Ala	335	340	345
Asp Pro Thr Lys Leu Glu Leu Leu Tyr Lys Ser Phe Lys Val Lys	350	355	360
Lys Glu Asp Phe Lys Glu Gln Gln Lys Glu Ser Ile Leu Glu Lys	365	370	375
Tyr Gly Gly Gln Glu His Leu Asp Ala Pro Pro Ala Glu Leu Leu	380	385	390
Leu Ala Gln Thr Glu Asp Tyr Val Glu Tyr Ser Arg His Gly Thr	395	400	405
Val Ile Lys Gly Gln Glu Arg Ala Val Ala Cys Ser Lys Tyr Glu	410	415	420
Glu Asp Val Lys Ile His Asn His Thr His Ile Trp Gly Ser Tyr	425	430	435
Trp Lys Glu Gly Arg Trp Gly Tyr Lys Cys Cys His Ser Phe Phe	440	445	450
Lys Tyr Ser Tyr Cys Thr Gly Glu Ala Gly Lys Glu Ile Val Asn	455	460	465
Ser Glu Glu Cys Ile Ile Asn Glu Ile Thr Gly Glu Glu Ser Val			

	470		475		480
Lys Lys Pro Gln Thr Leu Met Glu Leu His Gln Glu Lys Leu Lys					
	485		490		495
Glu Glu Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys His Arg Lys					
	500		505		510
Ser Ser Ser Asp Ser Asp Asp Glu Glu Lys Lys His Glu Lys Leu					
	515		520		525
Lys Lys Ala Leu Asn Ala Glu Glu Ala Arg Leu Leu His Val Lys					
	530		535		540
Glu Thr Met Gln Ile Asp Glu Arg Lys Arg Pro Tyr Asn Ser Met					
	545		550		555
Tyr Glu Thr Arg Glu Pro Thr Glu Glu Glu Met Glu Ala Tyr Arg					
	560		565		570
Met Lys Arg Gln Arg Pro Asp Asp Pro Met Ala Ser Phe Leu Gly					
	575		580		585
Gln					

<210> 9

<211> 384

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 2049352CD1

<400> 9

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp					
1	5		10		15
Thr Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg					
	20		25		30
Asn Thr Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser					
	35		40		45
Arg Pro Pro Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser					
	50		55		60
Glu Leu Lys Tyr His Pro Glu Met Arg Phe Phe His Trp Phe Ser					
	65		70		75
Lys Trp Arg Lys Leu His Arg Asp Gln Glu Tyr Glu Val Thr Trp					
	80		85		90
Tyr Ile Ser Trp Ser Pro Cys Thr Lys Cys Thr Arg Asp Met Ala					
	95		100		105
Thr Phe Leu Ala Glu Asp Pro Lys Val Thr Leu Thr Ile Phe Val					
	110		115		120
Ala Arg Leu Tyr Tyr Phe Trp Asp Pro Asp Tyr Gln Glu Ala Leu					
	125		130		135
Arg Ser Leu Cys Gln Lys Arg Asp Gly Pro Arg Ala Thr Met Lys					
	140		145		150
Ile Met Asn Tyr Asp Glu Phe Gln His Cys Trp Ser Lys Phe Val					
	155		160		165
Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn Asn Leu Pro Lys					
	170		175		180
Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile Leu Arg His					
	185		190		195
Ser Met Asp Pro Pro Thr Phe Thr Phe Asn Phe Asn Asn Glu Pro					
	200		205		210
Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val Glu					

215	220	225
Arg Met His Asn Asp Thr Trp Val Leu	Leu Asn Gln Arg Arg Gly	
230	235	240
Phe Leu Cys Asn Gln Ala Pro His Lys	His Gly Phe Leu Glu Gly	
245	250	255
Arg His Ala Glu Leu Cys Phe Leu Asp	Val Ile Pro Phe Trp Lys	
260	265	270
Leu Asp Leu Asp Gln Asp Tyr Arg Val	Thr Cys Phe Thr Ser Trp	
275	280	285
Ser Pro Cys Phe Ser Cys Ala Gln Glu	Met Ala Lys Phe Ile Ser	
290	295	300
Lys Asn Lys His Val Ser Leu Cys Ile	Phe Thr Ala Arg Ile Tyr	
305	310	315
Asp Asp Gln Gly Arg Cys Gln Glu Gly	Leu Arg Thr Leu Ala Glu	
320	325	330
Ala Gly Ala Lys Ile Ser Ile Leu Thr	Tyr Ser Glu Phe Lys His	
335	340	345
Cys Trp Asp Thr Phe Val Asp His Gln	Gly Cys Pro Phe Gln Pro	
350	355	360
Trp Asp Gly Leu Glu Glu His Ser Gln	Ala Leu Ser Gly Arg Leu	
365	370	375
Arg Gly Ile Leu Gln Asn Gln Gly Ser		
380		

<210> 10

<211> 325

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 2231663CD1

<400> 10

Met Ala Ala Ala Val Arg Cys Met Gly Arg Ala Leu Ile His His	
1 5 10 15	
Gln Arg His Ser Leu Ser Lys Met Val Tyr Gln Thr Ser Leu Cys	
20 25 30	
Ser Cys Ser Val Asn Ile Arg Val Pro Asn Arg His Phe Ala Ala	
35 40 45	
Ala Thr Lys Ser Ala Lys Lys Thr Lys Lys Gly Ala Lys Glu Lys	
50 55 60	
Thr Pro Asp Glu Lys Lys Asp Glu Ile Glu Lys Ile Lys Ala Tyr	
65 70 75	
Pro Tyr Met Glu Gly Glu Pro Glu Asp Asp Val Tyr Leu Lys Arg	
80 85 90	
Leu Tyr Pro Arg Gln Ile Tyr Glu Val Glu Lys Ala Val His Leu	
95 100 105	
Leu Lys Lys Phe Gln Ile Leu Asp Phe Thr Ser Pro Lys Gln Ser	
110 115 120	
Val Tyr Leu Asp Leu Thr Leu Asp Met Ala Leu Gly Lys Lys Lys	
125 130 135	
Asn Val Glu Pro Phe Thr Ser Val Leu Ser Leu Pro Tyr Pro Phe	
140 145 150	
Ala Ser Glu Ile Asn Lys Val Ala Val Phe Thr Glu Asn Ala Ser	
155 160 165	

Glu	Val	Lys	Ile	Ala	Glu	Glu	Asn	Gly	Ala	Ala	Phe	Ala	Gly	Gly
				170					175					180
Thr	Ser	Leu	Ile	Gln	Lys	Ile	Trp	Asp	Asp	Glu	Ile	Val	Ala	Asp
				185					190					195
Phe	Tyr	Val	Ala	Val	Pro	Glu	Ile	Met	Pro	Glu	Leu	Asn	Arg	Leu
				200					205					210
Arg	Lys	Lys	Leu	Asn	Lys	Lys	Tyr	Pro	Lys	Leu	Ser	Arg	Asn	Ser
				215					220					225
Ile	Gly	Arg	Asp	Ile	Pro	Lys	Met	Leu	Glu	Leu	Phe	Lys	Asn	Gly
				230					235					240
His	Glu	Ile	Lys	Val	Asp	Glu	Glu	Arg	Glu	Asn	Phe	Leu	Gln	Thr
				245					250					255
Lys	Ile	Ala	Thr	Leu	Asp	Met	Ser	Ser	Asp	Gln	Ile	Ala	Ala	Asn
				260					265					270
Leu	Gln	Ala	Val	Ile	Asn	Glu	Val	Cys	Arg	His	Arg	Pro	Leu	Asn
				275					280					285
Leu	Gly	Pro	Phe	Val	Val	Arg	Ala	Phe	Leu	Arg	Ser	Ser	Thr	Ser
				290					295					300
Glu	Gly	Leu	Leu	Leu	Lys	Ile	Asp	Pro	Leu	Leu	Pro	Lys	Glu	Val
				305					310					315
Lys	Asn	Glu	Glu	Ser	Glu	Lys	Glu	Asp	Ala					
				320					325					

<210> 11

<211> 351

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 2604449CD1

<400> 11

Met	Gly	Asp	Pro	Glu	Arg	Pro	Glu	Ala	Ala	Gly	Leu	Asp	Gln	Asp
1				5					10					15
Glu	Arg	Ser	Ser	Ser	Asp	Thr	Asn	Glu	Ser	Glu	Ile	Lys	Ser	Asn
				20					25					30
Glu	Glu	Pro	Leu	Leu	Arg	Lys	Ser	Ser	Arg	Arg	Phe	Val	Ile	Phe
				35					40					45
Pro	Ile	Gln	Tyr	Pro	Asp	Ile	Trp	Lys	Met	Tyr	Lys	Gln	Ala	Gln
				50					55					60
Ala	Ser	Phe	Trp	Thr	Ala	Glu	Glu	Val	Asp	Leu	Ser	Lys	Asp	Leu
				65					70					75
Pro	His	Trp	Asn	Lys	Leu	Lys	Ala	Asp	Glu	Lys	Tyr	Phe	Ile	Ser
				80					85					90
His	Ile	Leu	Ala	Phe	Phe	Ala	Ala	Ser	Asp	Gly	Ile	Val	Asn	Glu
				95					100					105
Asn	Leu	Val	Glu	Arg	Phe	Ser	Gln	Glu	Val	Gln	Val	Pro	Glu	Ala
				110					115					120
Arg	Cys	Phe	Tyr	Gly	Phe	Gln	Ile	Leu	Ile	Glu	Asn	Val	His	Ser
				125					130					135
Glu	Met	Tyr	Ser	Leu	Leu	Ile	Asp	Thr	Tyr	Ile	Arg	Asp	Pro	Lys
				140					145					150
Lys	Arg	Glu	Phe	Leu	Phe	Asn	Ala	Ile	Glu	Thr	Met	Pro	Tyr	Val
				155					160					165
Lys	Lys	Lys	Ala	Asp	Trp	Ala	Leu	Arg	Trp	Ile	Ala	Asp	Arg	Lys

170	175	180
Ser Thr Phe Gly Glu Arg Val Val Ala	Phe Ala Ala Val Glu Gly	
185	190	195
Val Phe Phe Ser Gly Ser Phe Ala Ala	Ile Phe Trp Leu Lys Lys	
200	205	210
Arg Gly Leu Met Pro Gly Leu Thr Phe	Ser Asn Glu Leu Ile Ser	
215	220	225
Arg Asp Glu Gly Leu His Cys Asp Phe	Ala Cys Leu Met Phe Gln	
230	235	240
Tyr Leu Val Asn Lys Pro Ser Glu Glu	Arg Val Arg Glu Ile Ile	
245	250	255
Val Asp Ala Val Lys Ile Glu Gln Glu	Phe Leu Thr Glu Ala Leu	
260	265	270
Pro Val Gly Leu Ile Gly Met Asn Cys	Ile Leu Met Lys Gln Tyr	
275	280	285
Ile Glu Phe Val Ala Asp Arg Leu Leu	Val Glu Leu Gly Phe Ser	
290	295	300
Lys Val Phe Gln Ala Glu Asn Pro Phe	Asp Phe Met Glu Asn Ile	
305	310	315
Ser Leu Glu Gly Lys Thr Asn Phe Phe	Glu Lys Arg Val Ser Glu	
320	325	330
Tyr Gln Arg Phe Ala Val Met Ala Glu	Thr Thr Asp Asn Val Phe	
335	340	345
Thr Leu Asp Ala Asp Phe		
350		

<210> 12

<211> 681

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 2604993CD1

<400> 12

Met Thr Ala Ser Pro Asp Tyr Leu Val	Val Leu Phe Gly Ile Thr
1	5 10 15
Ala Gly Ala Thr Gly Ala Lys Leu Gly	Ser Asp Glu Lys Glu Leu
20	25 30
Ile Leu Leu Phe Trp Lys Val Val Asp	Leu Ala Asn Lys Lys Val
35	40 45
Gly Gln Leu His Glu Val Leu Val Arg	Pro Asp Gln Leu Glu Leu
50	55 60
Thr Glu Asp Cys Lys Glu Glu Thr Lys	Ile Asp Val Glu Ser Leu
65	70 75
Ser Ser Ala Ser Gln Leu Asp Gln Ala	Leu Arg Gln Phe Asn Gln
80	85 90
Ser Val Ser Asn Glu Leu Asn Ile Gly	Val Gly Thr Ser Phe Cys
95	100 105
Leu Cys Thr Asp Gly Gln Leu His Val	Arg Gln Ile Leu His Pro
110	115 120
Glu Ala Ser Lys Lys Asn Val Leu Leu	Pro Glu Cys Phe Tyr Ser
125	130 135
Phe Phe Asp Leu Arg Lys Glu Phe Lys	Lys Cys Cys Pro Gly Ser
140	145 150

Pro Asp Ile Asp	Lys	Leu	Asp	Val	Ala	Thr	Met	Thr	Glu	Tyr	Leu	
	155					160					165	
Asn Phe Glu Lys	Ser	Ser	Ser	Val	Ser	Arg	Tyr	Gly	Ala	Ser	Gln	
	170					175					180	
Val Glu Asp Met	Gly	Asn	Ile	Ile	Leu	Ala	Met	Ile	Ser	Glu	Pro	
	185					190					195	
Tyr Asn His Arg	Phe	Ser	Asp	Pro	Glu	Arg	Val	Asn	Tyr	Lys	Phe	
	200					205					210	
Glu Ser Gly Thr	Cys	Ser	Lys	Met	Glu	Leu	Ile	Asp	Asp	Asn	Thr	
	215					220					225	
Val Val Arg Ala	Arg	Gly	Leu	Pro	Trp	Gln	Ser	Ser	Asp	Gln	Asp	
	230					235					240	
Ile Ala Arg Phe	Phe	Lys	Gly	Leu	Asn	Ile	Ala	Lys	Gly	Gly	Ala	
	245					250					255	
Ala Leu Cys Leu	Asn	Ala	Gln	Gly	Arg	Arg	Asn	Gly	Glu	Ala	Leu	
	260					265					270	
Val Arg Phe Val	Ser	Glu	Glu	His	Arg	Asp	Leu	Ala	Leu	Gln	Arg	
	275					280					285	
His Lys His His	Met	Gly	Thr	Arg	Tyr	Ile	Glu	Val	Tyr	Lys	Ala	
	290					295					300	
Thr Gly Glu Asp	Phe	Leu	Lys	Ile	Ala	Gly	Gly	Thr	Ser	Asn	Glu	
	305					310					315	
Val Ala Gln Phe	Leu	Ser	Lys	Glu	Asn	Gln	Val	Ile	Val	Arg	Met	
	320					325					330	
Arg Gly Leu Pro	Phe	Thr	Ala	Thr	Ala	Glu	Glu	Val	Val	Ala	Phe	
	335					340					345	
Phe Gly Gln His	Cys	Pro	Ile	Thr	Gly	Gly	Lys	Glu	Gly	Ile	Leu	
	350					355					360	
Phe Val Thr Tyr	Pro	Asp	Gly	Arg	Pro	Thr	Gly	Asp	Ala	Phe	Val	
	365					370					375	
Leu Phe Ala Cys	Glu	Glu	Tyr	Ala	Gln	Asn	Ala	Leu	Arg	Lys	His	
	380					385					390	
Lys Asp Leu Leu	Gly	Lys	Arg	Tyr	Ile	Glu	Leu	Phe	Arg	Ser	Thr	
	395					400					405	
Ala Ala Glu Val	Gln	Gln	Val	Leu	Asn	Arg	Phe	Ser	Ser	Ala	Pro	
	410					415					420	
Leu Ile Pro Leu	Pro	Thr	Pro	Pro	Ile	Ile	Pro	Val	Leu	Pro	Gln	
	425					430					435	
Gln Phe Val Pro	Pro	Thr	Asn	Val	Arg	Asp	Cys	Ile	Arg	Leu	Arg	
	440					445					450	
Gly Leu Pro Tyr	Ala	Ala	Thr	Ile	Glu	Asp	Ile	Leu	Asp	Phe	Leu	
	455					460					465	
Gly Glu Phe Ala	Thr	Asp	Ile	Arg	Thr	His	Gly	Val	His	Met	Val	
	470					475					480	
Leu Asn His Gln	Gly	Arg	Pro	Ser	Gly	Asp	Ala	Phe	Ile	Gln	Met	
	485					490					495	
Lys Ser Ala Asp	Arg	Ala	Phe	Met	Ala	Ala	Gln	Lys	Cys	His	Lys	
	500					505					510	
Lys Asn Met Lys	Asp	Arg	Tyr	Val	Glu	Val	Phe	Gln	Cys	Ser	Ala	
	515					520					525	
Glu Glu Met Asn	Phe	Val	Leu	Met	Gly	Gly	Thr	Leu	Asn	Arg	Asn	
	530					535					540	
Gly Leu Ser Pro	Pro	Pro	Cys	Lys	Leu	Pro	Cys	Leu	Ser	Pro	Pro	
	545					550					555	
Ser Tyr Thr Phe	Pro	Ala	Pro	Ala	Ala	Val	Ile	Pro	Thr	Glu	Ala	
	560					565					570	
Ala Ile Tyr Gln	Pro	Ser	Val	Ile	Leu	Asn	Pro	Arg	Ala	Leu	Gln	

575	580	585
Pro Ser Thr Ala Tyr Tyr Pro Ala Gly Thr Gln Leu Phe Met Asn		
590	595	600
Tyr Thr Ala Tyr Tyr Pro Ser Pro Pro Gly Ser Pro Asn Ser Leu		
605	610	615
Gly Tyr Phe Pro Thr Ala Ala Asn Leu Ser Gly Val Pro Pro Gln		
620	625	630
Pro Gly Thr Val Val Arg Met Gln Gly Leu Ala Tyr Asn Thr Gly		
635	640	645
Val Lys Glu Ile Leu Asn Phe Phe Gln Gly Tyr Gln Tyr Ala Thr		
650	655	660
Glu Asp Gly Leu Ile His Thr Asn Asp Gln Ala Arg Thr Leu Pro		
665	670	675
Lys Glu Trp Val Cys Ile		
680		

<210> 13

<211> 408

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 2879070CD1

<400> 13

Met Ser Ser Leu Val Glu Thr Phe Val Ser Lys Ala Ser Ala Leu		
1 5 10 15		
Gln Arg Gln Gly Arg Ala Gly Arg Val Arg Asp Gly Phe Cys Phe		
20 25 30		
Arg Met Tyr Thr Arg Glu Arg Phe Glu Gly Phe Met Asp Tyr Ser		
35 40 45		
Val Pro Glu Ile Leu Arg Val Pro Leu Glu Glu Leu Cys Leu His		
50 55 60		
Ile Met Lys Cys Asn Leu Gly Ser Pro Glu Asp Phe Leu Ser Lys		
65 70 75		
Ala Leu Asp Pro Pro Gln Leu Gln Val Ile Ser Asn Ala Met Asn		
80 85 90		
Leu Leu Arg Lys Ile Gly Ala Cys Glu Leu Asn Glu Pro Lys Leu		
95 100 105		
Thr Pro Leu Gly Gln His Leu Ala Ala Leu Pro Val Asn Val Lys		
110 115 120		
Ile Gly Lys Met Leu Ile Phe Gly Ala Ile Phe Gly Cys Leu Asp		
125 130 135		
Pro Val Ala Thr Leu Ala Ala Val Met Thr Glu Lys Ser Pro Phe		
140 145 150		
Thr Thr Pro Ile Gly Arg Lys Asp Glu Ala Asp Leu Ala Lys Ser		
155 160 165		
Ala Leu Ala Met Ala Asp Ser Asp His Leu Thr Ile Tyr Asn Ala		
170 175 180		
Tyr Leu Gly Trp Lys Lys Ala Arg Gln Glu Gly Gly Tyr Arg Ser		
185 190 195		
Glu Ile Thr Tyr Cys Arg Arg Asn Phe Leu Asn Arg Thr Ser Leu		
200 205 210		
Leu Thr Leu Glu Asp Val Lys Gln Glu Leu Ile Lys Leu Val Lys		
215 220 225		

Ala	Ala	Gly	Phe	Ser	Ser	Ser	Thr	Thr	Ser	Thr	Ser	Trp	Glu	Gly	
				230					235					240	
Asn	Arg	Ala	Ser	Gln	Thr	Leu	Ser	Phe	Gln	Glu	Ile	Ala	Leu	Leu	
				245					250					255	
Lys	Ala	Val	Leu	Val	Ala	Gly	Leu	Tyr	Asp	Asn	Val	Gly	Lys	Ile	
				260					265					270	
Ile	Tyr	Thr	Lys	Ser	Val	Asp	Val	Thr	Glu	Lys	Leu	Ala	Cys	Ile	
				275					280					285	
Val	Glu	Thr	Ala	Gln	Gly	Lys	Ala	Gln	Val	His	Pro	Ser	Ser	Val	
				290					295					300	
Asn	Arg	Asp	Leu	Gln	Thr	His	Gly	Trp	Leu	Leu	Tyr	Gln	Glu	Lys	
				305					310					315	
Ile	Arg	Tyr	Ala	Arg	Val	Tyr	Leu	Arg	Glu	Thr	Thr	Leu	Ile	Thr	
				320					325					330	
Pro	Phe	Pro	Val	Leu	Leu	Phe	Gly	Gly	Asp	Ile	Glu	Val	Gln	His	
				335					340					345	
Arg	Glu	Arg	Leu	Leu	Ser	Ile	Asp	Gly	Trp	Ile	Tyr	Phe	Gln	Ala	
				350					355					360	
Pro	Val	Lys	Ile	Ala	Val	Ile	Phe	Lys	Gln	Leu	Arg	Val	Leu	Ile	
				365					370					375	
Asp	Ser	Val	Leu	Arg	Lys	Lys	Leu	Glu	Asn	Pro	Lys	Met	Ser	Leu	
				380					385					390	
Glu	Asn	Asp	Lys	Ile	Leu	Gln	Ile	Ile	Thr	Glu	Leu	Ile	Lys	Thr	
				395					400					405	

Glu Asn Asn

<210> 14
 <211> 351
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No.: 3093845CD1

<400> 14

Met	Ile	Pro	Lys	Ser	Tyr	Thr	Glu	Glu	Asp	Leu	Arg	Glu	Lys	Phe	
				5					10					15	
Lys	Val	Tyr	Gly	Asp	Ile	Glu	Tyr	Cys	Ser	Ile	Ile	Lys	Asn	Lys	
				20					25					30	
Val	Thr	Gly	Glu	Ser	Lys	Gly	Leu	Gly	Tyr	Val	Arg	Tyr	Leu	Lys	
				35					40					45	
Pro	Ser	Gln	Ala	Ala	Gln	Ala	Ile	Glu	Asn	Cys	Asp	Arg	Ser	Phe	
				50					55					60	
Arg	Ala	Ile	Leu	Ala	Glu	Pro	Lys	Asn	Lys	Ala	Ser	Glu	Ser	Ser	
				65					70					75	
Glu	Gln	Asp	Tyr	Tyr	Ser	Asn	Met	Arg	Gln	Glu	Ala	Leu	Gly	His	
				80					85					90	
Glu	Pro	Arg	Val	Asn	Met	Phe	Pro	Phe	Val	Gly	Glu	Gln	Gln	Ser	
				95					100					105	
Glu	Phe	Ser	Ser	Phe	Asp	Lys	Asn	Asp	Ser	Arg	Gly	Gln	Glu	Ala	
				110					115					120	
Ile	Ser	Lys	Arg	Leu	Ser	Val	Val	Ser	Arg	Val	Pro	Phe	Thr	Glu	
				125					130					135	

Glu Gln Leu Phe Ser Ile Phe Asp Ile Val Pro Gly Leu Glu Tyr

	140		145		150
Cys Glu Val Gln Arg Asp Pro Tyr Ser Asn Tyr Gly His Gly Val					
	155		160		165
Val Gln Tyr Phe Asn Val Ala Ser Ala Ile Tyr Ala Lys Tyr Lys					
	170		175		180
Leu His Gly Phe Gln Tyr Pro Pro Gly Asn Arg Ile Gly Val Ser					
	185		190		195
Phe Ile Asp Asp Gly Ser Asn Ala Thr Asp Leu Leu Arg Lys Met					
	200		205		210
Ala Thr Gln Met Val Ala Ala Gln Leu Ala Ser Met Val Trp Asn					
	215		220		225
Asn Pro Ser Gln Gln Gln Phe Met Gln Phe Gly Gly Ser Ser Gly					
	230		235		240
Ser Gln Leu Pro Gln Ile Gln Thr Asp Val Val Leu Pro Ser Cys					
	245		250		255
Lys Lys Lys Ala Pro Ala Glu Thr Pro Val Lys Glu Arg Leu Phe					
	260		265		270
Ile Val Phe Asn Pro His Pro Leu Pro Leu Asp Val Leu Glu Asp					
	275		280		285
Ile Phe Cys Arg Phe Gly Asn Leu Ile Glu Val Tyr Leu Val Ser					
	290		295		300
Gly Lys Asn Val Gly Tyr Ala Lys Tyr Ala Asp Arg Ile Ser Ala					
	305		310		315
Asn Asp Ala Ile Ala Thr Leu His Gly Lys Ile Leu Asn Gly Val					
	320		325		330
Arg Leu Lys Val Met Leu Ala Asp Ser Pro Arg Glu Glu Ser Asn					
	335		340		345
Lys Arg Gln Arg Thr Tyr					
	350				

<210> 15

<211> 472

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 3685685CD1

<400> 15

Met Gly Gln Ser Gly Arg Ser Arg His Gln Lys Arg Ala Arg Ala		
1	5	10
Gln Ala Gln Leu Arg Asn Leu Glu Ala Tyr Ala Ala Asn Pro His		
	20	25
Ser Phe Val Phe Thr Arg Gly Cys Thr Gly Arg Asn Ile Arg Gln		
	35	40
Leu Ser Leu Asp Val Arg Arg Val Met Glu Pro Leu Thr Ala Ser		
	50	55
Arg Leu Gln Val Arg Lys Lys Asn Ser Leu Lys Asp Cys Val Ala		
	65	70
Val Ala Gly Pro Leu Gly Val Thr His Phe Leu Ile Leu Ser Lys		
	80	85
Thr Glu Thr Asn Val Tyr Phe Lys Leu Met Arg Leu Pro Gly Gly		
	95	100
Pro Thr Leu Thr Phe Gln Val Lys Lys Tyr Ser Leu Val Arg Asp		
	110	115
		120

Val	Val	Ser	Ser	Leu	Arg	Arg	His	Arg	Met	His	Glu	Gln	Gln	Phe
				125					130					135
Ala	His	Pro	Pro	Leu	Leu	Val	Leu	Asn	Ser	Phe	Gly	Pro	His	Gly
				140					145					150
Met	His	Val	Lys	Leu	Met	Ala	Thr	Met	Phe	Gln	Asn	Leu	Phe	Pro
				155					160					165
Ser	Ile	Asn	Val	His	Lys	Val	Asn	Leu	Asn	Thr	Ile	Lys	Arg	Cys
				170					175					180
Leu	Leu	Ile	Asp	Tyr	Asn	Pro	Asp	Ser	Gln	Glu	Leu	Asp	Phe	Arg
				185					190					195
His	Tyr	Ile	Lys	Val	Val	Pro	Val	Gly	Ala	Ser	Arg	Gly	Met	Lys
				200					205					210
Lys	Leu	Leu	Gln	Glu	Lys	Phe	Pro	Asn	Met	Ser	Arg	Leu	Gln	Asp
				215					220					225
Ile	Ser	Glu	Leu	Leu	Ala	Thr	Gly	Ala	Gly	Leu	Ser	Glu	Ser	Glu
				230					235					240
Ala	Glu	Pro	Asp	Gly	Asp	His	Asn	Ile	Thr	Glu	Leu	Pro	Gln	Ala
				245					250					255
Val	Ala	Gly	Arg	Gly	Asn	Met	Arg	Ala	Gln	Gln	Ser	Ala	Val	Arg
				260					265					270
Leu	Thr	Glu	Ile	Gly	Pro	Arg	Met	Thr	Leu	Gln	Leu	Ile	Lys	Val
				275					280					285
Gln	Glu	Gly	Val	Gly	Glu	Gly	Lys	Val	Met	Phe	His	Ser	Phe	Val
				290					295					300
Ser	Lys	Thr	Glu	Glu	Glu	Leu	Gln	Ala	Ile	Leu	Glu	Ala	Lys	Glu
				305					310					315
Lys	Lys	Leu	Arg	Leu	Lys	Ala	Gln	Arg	Gln	Ala	Gln	Gln	Ala	Gln
				320					325					330
Asn	Val	Gln	Arg	Lys	Gln	Glu	Gln	Arg	Glu	Ala	His	Arg	Lys	Lys
				335					340					345
Ser	Leu	Glu	Gly	Met	Lys	Lys	Ala	Arg	Val	Gly	Gly	Ser	Asp	Glu
				350					355					360
Glu	Ala	Ser	Gly	Ile	Pro	Ser	Arg	Thr	Ala	Ser	Leu	Glu	Leu	Gly
				365					370					375
Glu	Asp	Asp	Asp	Glu	Gln	Glu	Asp	Asp	Asp	Ile	Glu	Tyr	Phe	Cys
				380					385					390
Gln	Ala	Val	Gly	Glu	Ala	Pro	Ser	Glu	Asp	Leu	Phe	Pro	Glu	Ala
				395					400					405
Lys	Gln	Lys	Arg	Leu	Ala	Lys	Ser	Pro	Gly	Arg	Lys	Arg	Lys	Arg
				410					415					420
Trp	Glu	Met	Asp	Arg	Gly	Arg	Gly	Arg	Leu	Cys	Asp	Gln	Lys	Phe
				425					430					435
Pro	Lys	Thr	Lys	Asp	Lys	Ser	Gln	Gly	Ala	Gln	Ala	Arg	Arg	Gly
				440					445					450
Pro	Arg	Gly	Ala	Ser	Arg	Asp	Gly	Gly	Arg	Gly	Arg	Gly	Arg	Gly
				455					460					465
Arg	Pro	Gly	Lys	Arg	Val	Ala								
				470										

<210> 16

<211> 616

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 3825977CD1

<400> 16

Met	Ser	Ser	Leu	Ala	Val	Arg	Asp	Pro	Ala	Met	Asp	Arg	Ser	Leu	1	5	10	15
Arg	Ser	Val	Phe	Val	Gly	Asn	Ile	Pro	Tyr	Glu	Ala	Thr	Glu	Glu	20	25	30	35
Gln	Leu	Lys	Asp	Ile	Phe	Ser	Glu	Val	Gly	Ser	Val	Val	Ser	Phe	40	45	50	55
Arg	Leu	Val	Tyr	Asp	Arg	Glu	Thr	Gly	Lys	Pro	Lys	Gly	Tyr	Gly	60	65	70	75
Phe	Cys	Glu	Tyr	Gln	Asp	Gln	Glu	Thr	Ala	Leu	Ser	Ala	Met	Arg	80	85	90	95
Asn	Leu	Asn	Gly	Arg	Glu	Phe	Ser	Gly	Arg	Ala	Leu	Arg	Val	Asp	100	105	110	115
Asn	Ala	Ala	Ser	Glu	Lys	Asn	Lys	Glu	Glu	Leu	Lys	Ser	Leu	Gly	120	125	130	135
Pro	Ala	Ala	Pro	Ile	Ile	Asp	Ser	Pro	Tyr	Gly	Asp	Pro	Ile	Asp	140	145	150	155
Pro	Glu	Asp	Ala	Pro	Glu	Ser	Ile	Thr	Arg	Ala	Val	Ala	Ser	Leu	160	165	170	175
Pro	Pro	Glu	Gln	Met	Phe	Glu	Leu	Met	Lys	Gln	Met	Lys	Leu	Cys	180	185	190	195
Val	Gln	Asn	Ser	His	Gln	Glu	Ala	Arg	Asn	Met	Leu	Leu	Gln	Asn	200	205	210	215
Pro	Gln	Leu	Ala	Tyr	Ala	Leu	Leu	Gln	Ala	Gln	Val	Val	Met	Arg	220	225	230	235
Ile	Met	Asp	Pro	Glu	Ile	Ala	Leu	Lys	Ile	Leu	His	Arg	Lys	Ile	240	245	250	255
His	Val	Thr	Pro	Leu	Ile	Pro	Gly	Lys	Ser	Gln	Ser	Val	Ser	Val	260	265	270	275
Ser	Gly	Pro	Gly	Pro	Gly	Pro	Gly	Pro	Gly	Leu	Cys	Pro	Gly	Pro	280	285	290	295
Asn	Val	Leu	Leu	Asn	Gln	Gln	Asn	Pro	Pro	Ala	Pro	Gln	Pro	Gln	300	305	310	315
His	Leu	Ala	Arg	Arg	Pro	Val	Lys	Asp	Ile	Pro	Pro	Leu	Met	Gln	320	325	330	335
Thr	Pro	Ile	Gln	Gly	Gly	Ile	Pro	Ala	Pro	Gly	Pro	Ile	Pro	Ala	340	345	350	355
Ala	Val	Pro	Gly	Ala	Gly	Pro	Gly	Ser	Leu	Thr	Pro	Gly	Gly	Ala	360	365	370	375
Met	Gln	Pro	Gln	Leu	Gly	Met	Pro	Gly	Val	Gly	Pro	Val	Pro	Leu	380	385	390	
Glu	Arg	Gly	Gln	Val	Gln	Met	Ser	Asp	Pro	Arg	Ala	Pro	Ile	Pro				
Arg	Gly	Pro	Val	Thr	Pro	Gly	Gly	Leu	Pro	Pro	Arg	Gly	Leu	Leu				
Gly	Asp	Ala	Pro	Asn	Asp	Pro	Arg	Gly	Gly	Thr	Leu	Leu	Ser	Val				
Thr	Gly	Glu	Val	Glu	Pro	Arg	Gly	Tyr	Leu	Gly	Pro	Pro	His	Gln				
Gly	Pro	Pro	Met	His	His	Ala	Ser	Gly	His	Asp	Thr	Arg	Gly	Pro				
Ser	Ser	His	Glu	Met	Arg	Gly	Gly	Pro	Leu	Gly	Asp	Pro	Arg	Leu				

Leu Ile Gly Glu Pro Arg Gly Pro Met Ile Asp Gln Arg Gly Leu
 395 400 405
 Pro Met Asp Gly Arg Gly Gly Arg Asp Ser Arg Ala Met Glu Thr
 410 415 420
 Arg Ala Met Glu Thr Glu Val Leu Glu Thr Arg Val Met Glu Arg
 425 430 435
 Arg Gly Met Glu Thr Cys Ala Met Glu Thr Arg Gly Met Glu Ala
 440 445 450
 Arg Gly Met Asp Ala Arg Gly Leu Glu Met Arg Gly Pro Val Pro
 455 460 465
 Ser Ser Arg Gly Pro Met Thr Gly Gly Ile Gln Gly Pro Gly Pro
 470 475 480
 Ile Asn Ile Gly Ala Gly Gly Pro Pro Gln Gly Pro Arg Gln Val
 485 490 495
 Pro Gly Ile Ser Gly Val Gly Asn Pro Gly Ala Gly Met Gln Gly
 500 505 510
 Thr Gly Ile Gln Gly Thr Gly Met Gln Gly Ala Gly Ile Gln Gly
 515 520 525
 Gly Gly Met Gln Gly Ala Gly Ile Gln Gly Val Ser Ile Gln Gly
 530 535 540
 Gly Gly Ile Gln Gly Gly Gly Ile Gln Gly Ala Ser Lys Gln Gly
 545 550 555
 Gly Ser Gln Pro Ser Ser Phe Ser Pro Gly Gln Ser Gln Val Thr
 560 565 570
 Pro Gln Asp Gln Glu Lys Ala Ala Leu Ile Met Gln Val Leu Gln
 575 580 585
 Leu Thr Ala Asp Gln Ile Ala Met Leu Pro Pro Glu Gln Arg Gln
 590 595 600
 Ser Ile Leu Ile Leu Lys Glu Gln Ile Gln Lys Ser Thr Gly Ala
 605 610 615
 Ser

<210> 17
 <211> 112
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No.: 4941262CD1

<400> 17
 Met Val Lys Gly Arg Thr Gly Gln Arg Val Arg Leu Tyr Val Arg
 1 5 10 15
 Gly Thr Ile Leu Gly Tyr Lys Arg Ser Lys Ser Asn Gln Tyr Glu
 20 25 30
 Thr Thr Ser Leu Ile Gln Ile Glu Gly Val Asn Thr Lys Glu Asp
 35 40 45
 Val Ala Trp Tyr Ala Gly Lys Arg Met Ala Tyr Ile Tyr Lys Ala
 50 55 60
 Lys Thr Lys Ser Ser Glu Thr Arg Tyr Arg Cys Ile Trp Gly Lys
 65 70 75
 Val Thr Arg Pro His Gly Asn Ser Gly Val Val Arg Ala Lys Phe
 80 85 90
 Lys Ser Asn Leu Pro Pro Glu Ser Met Gly Arg Lys Val Arg Val
 95 100 105

Phe Met Tyr Pro Ser Ser Ile
110

<210> 18
<211> 1872
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
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<213> Homo sapiens

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<211> 2596

<212> DNA

<213> Homo sapiens

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cttgcatgtt ggagacggcc caaggcaaag cacaagtaca cccatcctca gtaaatcgag 1200
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ttgaaaatcc aaagatgtcc cttgaaaatg acaagattct gcagatcatt acggaattga 1500
taaaaaacaga gaataactga aactgaaatt catgggtcaac tgctttaaaaa attaatgata 1560
agatacagtc atgaaattat ctgaaaatgg gtcatacacat taagtatttc attacttaaa 1620
atgttggtag tagccattaa cttaaagggtg gtgggaaaaa agcacatact ttaaacatgt 1680
ataattttct agttcctttt taatgatgat tattctgaat gtatttgcca ctacatttac 1740
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<210> 31

<211> 1382

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 3093845CB1

<400> 31

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tggaagtcac cgagatgttg aagatgaaga acttacaaga atctttgtta tgataccaaa 60
gtcctacaca gaagaagatc tgcgggaaaa atttaaggtg tatggagata tcgagtattg 120
cagcattatt aagaataaag tgactggaga aagtaaaggt ttgggctacg tacgatactt 180
aaaaccatca caagctgccc aagcaataga aaactgtgat cgaagtttta gagcaatctt 240
ggctgaacct aaaaataaag catctgaatc ctctgaacaa gattattata gtaatatgag 300
gcaagaagct ttgggacatg aacctagagt aaatatgttt ccatttgtcg gagaacaaca 360
atctgaattt tcaagttttg acaagaatga tagccgaggc caggaagcaa tctccaaacg 420
cttgtcagtt gtatcaagag ttcctttcac tgaagaacag cttttcagca tttttgatat 480
agtaccagga ttggaatatt gtgaagttca acgagatcct tattcaaatt atggtcattg 540
agtgttcag tattttaatg tagcatcagc tatttatgca aaatacaaat tacatggatt 600
tcagtaccct cctgggaacc gaataggtgt ttccttcatt gatgatggaa gtaatgcaac 660
agatctcctt agaaaaatgg caacacagat ggtagctgca cagcttgcac caatgggtg 720
gaataaccca agtcagcaac aatttatgca atttggagga agctctggat cacagttgcc 780
tcaaatccag acagatgttg tacttccatc atgcaaaaaa aaagctcctg ctgaaactcc 840
tgtgaaagaa agacttttta ttgtgtttta tcctcatcct ttacctttag acgtattaga 900
agatatattc tgtcgttttg gtaacctgat cgaagtttac cttgtgtcag gaaaaaatgt 960
ggggtatgcc aagtatgcc atagaataag tgctaagat gccattgcc ctctacatgg 1020
aaagattctg aatgggggtga gacttaaggt tatgctggca gattcgccaa gagaagaatc 1080
taacaaaacg caaagaactt actgattctt gagaacaaag actaaataat gacataatcc 1140
tcagctgact gactgaaaat gtgactggac gcattccctg tggacagttg acagcttttt 1200
tttttttcca tatacctgat agtctgtgta cagcattgtt ttgtctggga agcagggatt 1260
gctgacatgt atttttgaat ccatacatta atgctaaaac gaatatagta gttgttcctt 1320
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<210> 32

<211> 1828

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 3685685CB1

<400> 32

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gcgcgccgcg gccagggcgc agctccgcaa cctcgaggcc tatgccgcga acccgcactc 180
gttcgtgttc acgcgaggct gcacgggtcg caacatccgg cagctcagcc tggacgtgcg 240
gcgggtcatg gagccgctca ctgccagccg tctgcaggtt cgtaagaaga actcgctgaa 300
ggactgcgtg gcagtggctg ggccccctcg ggtcacacac tttctgatcc tgagcaaaaac 360
agagaccaat gtctacttta agctgatgcg cctcccagga ggccccacct tgaccttcca 420
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cgagcagcag tttgcccacc caccctcctt ggtactcaac agctttggcc cccatgggtat 540
gcatgtgaag ctcatggcca ccatgttcca gaacctgttc ccctccatca acgtgcacaa 600
ggtgaacctg aacaccatca agcgctgcct cctcatcgac tacaatcccg actcccagga 660
gctggacttc cgccactaca tcaaagttgt tctgtgggc gcgagtcgcg ggatgaagaa 720
gctgctccag gagaagttcc ccaacatgag ccgcctgcag gacatcagcg agctgctggc 780
cacgggcgcg gggctgtcgc agagcgaggc agagcctgac ggcgaccaca acatcacaga 840
gctgcctcag gctgtcgctg gccgtggcaa catgcggggc cagcagagtg cagtgcggct 900
caccgagatc ggccccgcga tgacactgca gctcatcaag gtccaggagg gcgtcgggga 960

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gggcaaagtg atgttccaca gttttgtgag caagacggag gaggagctgc aggccatcct 1020
ggaagccaag gagaagaagc tgcggctgaa ggcgagagg caggcccagc agggccagaa 1080
tgtgcagcgc aagcaggagc agcgggaggg ccacagaaag aagagcctgg agggcatgaa 1140
gaaggcacgg gtccgggggta gtgatgaaga ggcctctggg atcccttcaa ggacggcgag 1200
cctggagttg ggtgaggacg atgatgaaca ggaagatgat gacatcgagt atttctgcca 1260
ggcgggtgggc gaggcgcccc gtgaggacct gttccccgag gccaagcaga aacggcttgc 1320
caagtctcca gggcggaagc ggaagcgggt ggaaatggat cgaggcaggg gtcgcctttg 1380
tgaccagaag tttccaaga ccaaggacaa gtcccaggga gcccaggcca ggcggggggc 1440
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ggcctgagcc caagccgcac cggagcagcg gctggattga acgcccaga ttggggcccg 1560
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acaaagcaac ccagagagtc ctgggcccgc cacaccgag agtccctccc acctggtttc 1740
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cagccatgag tggccctccc cccagtcc

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<210> 33

<211> 2602

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 3825977CB1

<400> 33

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atgaaggatc agggactgaa agcattagat aagttgttag tgggatgcag gttccacagg 120
caagcggaaac gattcaagcg aattagtaaa gtttctgccc ggatcttgaa agccgcttcc 180
gttgetcagc ggaagtgtcg gtgcgaagag gacagacgcc tcgaagaatc cgtatcggc 240
tgtctgcaca accggaatca tgcgagttt ggcggtgaga gaccggcaa tggatcgatc 300
actgcgttcc gtgttcgtgg ggaacattcc atatgaggca actgaggagc agttaaagga 360
cattttctcg gaggttgggt ctgttgtcag tttccggctg gtatacgata gagagacggg 420
aaaacccaag ggctatggct tctgcgaata ccaagaccag gagaccgcgc ttagtgccat 480
gcggaacctc aatggggcgg agttcagtgg gagagcgctt cgggtggaca atgctgccag 540
tgaaaaagaat aaggaggagt taaagagcct tgggcctgca gcgcccatta ttgactcacc 600
ctatggggat cccatcgatc cagaagatgc ccctgaatcg attaccagag cagtagccag 660
tctccccccg gagcagatgt ttgagctgat gaagcagatg aagctctgtg tccaaaacag 720
ccaccaggaa gctcgaaaca tgttacttca aaatccacaa ctggcttatg cactgttgca 780
ggcacaagta gtgatgagaa tcatggatcc agagattgct ctgaaaattc tgcacggaa 840
gatacatgtc acaccactga tcccaggcaa atctcagttc gtgtctgtct ctggccctgg 900
ccctggccct ggccctgggc tctgccagg acctaattgt ctgtgaacc agcagaatcc 960
tccagctcct cagcctcagc atttggttag aagacctgtg aaggacattc ctctctgat 1020
gcagactcct atccagggtg gaattccagc tccagggcca ataccagctg cagtccccg 1080
agctgggtcct ggttccttaa ctctggagg agcaatgcag ccccaacttg gaatgccag 1140
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acctcgcgga cccgtgactc ctggtggtct gcctcctcga ggactgttag gagatgctcc 1260
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gcccagaggc cccatgatag atcaaagggg tctacctatg gatggtagag gtggtagaga 1500
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aattcagggc cctggtccca ttaatatagg ggcaggtggc cctcctcagg gaccagaca 1740
ggtcccaggc atttcagggg tggggaatcc tggagctggt atgcagggtg caggcataca 1800

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aggaacaggc atgcaggag caggcataca aggaggagg atgcagggg caggcataca 1860
aggagtcagt atacaaggag gaggtataca aggaggagg atacagggg caagcaagca 1920
aggtggaagc cagcctagca gtttttagtc tgggcagagc caggtcactc cacaggatca 1980
ggagaaggca gctttgatca tgcagggtct tcaactgact gcagatcaga ttgccatgct 2040
gccccctgag caaaggcaga gtatcctgat tttaaaggaa caaatccaga aatccactgg 2100
agcgtcttga aagggttttag aaaatatatt gctgtagtct caaattttat tctgtagcat 2160
ggagaatggg tgcaaaaagc tgactttctgt atccccacac ttggattagg gtttccctcc 2220
tcctagaacc taatcttatt ttttgttctt tttctttctt tctgttttcc tttttttttt 2280
aattgagggt ggggggagga gggagtgcgt ctgttcactt taagttactt taaaataact 2340
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tctacagtat gttaactaca ttttttaaat gtcgagtaaa acttcgtgaa aactgctcat 2460
aaagactaaa agttgacctg ttaaaacgtt aatgtactaa gatagtttta agatttttgg 2520
ttgtataaca aaataaaagt ttacccaaaa gtaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2580
aaaaaaaaaa aaaaaaaaaa aa                                     2602

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<210> 34

<211> 566

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 4941262CB1

<400> 34

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gcagaagtgg aaggaagcag gcggccacca tgggtgaagg acgcacggga cagcgcgctca 60
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ccacgtcgct cattcagatc gaggggggtga acaccaagga ggacgtcgcg tggtagctg 180
gcaagcgcat ggcgtacatc tacaaggcta agaccaagag cagcgagacc cgctacaggt 240
gcatctgggg caaggtcacc cgcccgcacg gcaactcggg cgtcgtccgc gccaaagttca 300
agtccaacct cccgcctgag tccatggggc gcaagggtcag agtgttcatg taccogagca 360
gcatctaagg tttttgttgg agtaaagggt gactctaaat ggccatgctt agttcttctc 420
tctgagctta aaatgccatg tggtggcaac ttagattgtt catgtactga acctgttgaa 480
gttctaccaa aatttgttgt cgaacggctg aacagttgtc ctaatgttat gctataaaca 540
gagcttattt caaaaaaaaa aaaaaa                                     566

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<210> 35

<211> 183

<212> PRT

<213> Homo sapiens

<300>

<308> Incyte ID No.: g2961149

<400> 35

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Met Ser Arg Tyr Leu Arg Pro Pro Asn Thr Ser Leu Phe Val Arg
  1          5          10          15
Asn Val Ala Asp Asp Thr Arg Ser Glu Asp Leu Arg Arg Glu Phe
          20          25          30
Gly Arg Tyr Gly Pro Ile Val Asp Val Tyr Val Pro Leu Asp Phe
          35          40          45
Tyr Thr Arg Arg Pro Arg Gly Phe Ala Tyr Val Gln Phe Glu Asp
          50          55          60
Val Arg Asp Ala Glu Asp Ala Leu His Asn Leu Asp Arg Lys Trp

```

	65		70		75
Ile Cys Gly Arg	Gln Ile Glu Ile Gln	Phe Ala Gln Gly Asp Arg			
	80		85		90
Lys Thr Pro Asn	Gln Met Lys Ala Lys	Glu Gly Arg Asn Val Tyr			
	95		100		105
Ser Ser Ser Arg	Tyr Asp Asp Tyr Asp	Arg Tyr Arg Arg Ser Arg			
	110		115		120
Ser Arg Ser Tyr	Glu Arg Arg Arg Ser	Arg Ser Arg Ser Phe Asp			
	125		130		135
Tyr Asn Tyr Arg	Arg Ser Tyr Ser Pro	Arg Asn Ser Arg Pro Thr			
	140		145		150
Gly Arg Pro Arg	Arg Ser Arg Ser His	Ser Asp Asn Asp Arg Pro			
	155		160		165
Asn Cys Ser Trp	Asn Thr Gln Tyr Ser	Ser Ala Tyr Tyr Thr Ser			
	170		175		180
Arg Lys Ile					

<210> 36

<211> 1404

<212> PRT

<213> Homo sapiens

<300>

<308> Incyte ID No.: g2660712

<400> 36

Met Ser Gly Ala Arg	Thr Ala Ser Thr	Pro Thr Pro Pro	Gln Thr	
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Gly Gly Gly Leu	Glu Pro Gln Ala Asn	Gly Glu Thr Pro	Gln Val	
	20	25	30	
Ala Val Ile Val	Arg Pro Asp Asp Arg	Ser Gln Gly Ala	Ile Ile	
	35	40	45	
Ala Asp Arg Pro	Gly Leu Pro Gly Pro	Glu His Ser Pro	Ser Glu	
	50	55	60	
Ser Gln Pro Ser	Ser Pro Ser Pro Thr	Pro Ser Pro Ser	Pro Val	
	65	70	75	
Leu Glu Pro Gly	Ser Glu Pro Asn Leu	Ala Val Leu Ser	Ile Pro	
	80	85	90	
Gly Asp Thr Met	Thr Thr Ile Gln Met	Ser Val Glu Glu	Ser Thr	
	95	100	105	
Pro Ile Ser Arg	Glu Thr Gly Glu Pro	Tyr Arg Leu Ser	Pro Glu	
	110	115	120	
Pro Thr Pro Leu	Ala Glu Pro Ile Leu	Glu Val Glu Val	Thr Leu	
	125	130	135	
Ser Lys Pro Val	Pro Glu Ser Glu Phe	Ser Ser Ser Pro	Leu Gln	
	140	145	150	
Ala Pro Thr Pro	Leu Ala Ser His Thr	Val Glu Ile His	Glu Pro	
	155	160	165	
Asn Gly Met Val	Pro Ser Glu Asp Leu	Glu Pro Glu Val	Glu Ser	
	170	175	180	
Ser Pro Glu Leu	Ala Pro Pro Pro Ala	Cys Pro Ser Glu	Ser Pro	
	185	190	195	
Val Pro Ile Ala	Pro Thr Ala Gln Pro	Glu Glu Leu Leu	Asn Gly	
	200	205	210	
Ala Pro Ser Pro	Pro Ala Val Asp Leu	Ser Pro Val Ser	Glu Pro	
	215	220	225	

Glu	Glu	Gln	Ala	Lys	Glu	Val	Thr	Ala	Ser	Val	Ala	Pro	Pro	Thr	230	235	240
Ile	Pro	Ser	Ala	Thr	Pro	Ala	Thr	Ala	Pro	Ser	Ala	Thr	Ser	Pro	245	250	255
Ala	Gln	Glu	Glu	Glu	Met	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Gly	260	265	270
Glu	Ala	Gly	Glu	Ala	Gly	Glu	Ala	Glu	Ser	Glu	Lys	Gly	Gly	Glu	275	280	285
Glu	Leu	Leu	Pro	Pro	Glu	Ser	Thr	Pro	Ile	Pro	Ala	Asn	Leu	Ser	290	295	300
Gln	Asn	Leu	Glu	Ala	Ala	Ala	Ala	Thr	Gln	Val	Ala	Val	Ser	Val	305	310	315
Pro	Lys	Arg	Arg	Arg	Lys	Ile	Lys	Glu	Leu	Asn	Lys	Lys	Glu	Ala	320	325	330
Val	Gly	Asp	Leu	Leu	Asp	Ala	Phe	Lys	Glu	Ala	Asn	Pro	Ala	Val	335	340	345
Pro	Glu	Val	Glu	Asn	Gln	Pro	Pro	Ala	Gly	Ser	Asn	Pro	Gly	Pro	350	355	360
Glu	Ser	Glu	Gly	Ser	Gly	Val	Pro	Pro	Arg	Pro	Glu	Glu	Ala	Asp	365	370	375
Glu	Thr	Trp	Asp	Ser	Lys	Glu	Asp	Lys	Ile	His	Asn	Ala	Glu	Asn	380	385	390
Ile	Gln	Pro	Gly	Glu	Gln	Lys	Tyr	Glu	Tyr	Lys	Ser	Asp	Gln	Trp	395	400	405
Lys	Pro	Pro	Asn	Leu	Glu	Glu	Lys	Lys	Arg	Tyr	Asp	Arg	Glu	Phe	410	415	420
Leu	Leu	Gly	Phe	Gln	Phe	Ile	Phe	Ala	Ser	Met	Gln	Lys	Pro	Glu	425	430	435
Gly	Leu	Pro	His	Ile	Ser	Asp	Val	Val	Leu	Asp	Lys	Ala	Asn	Lys	440	445	450
Thr	Pro	Leu	Arg	Pro	Leu	Asp	Pro	Thr	Arg	Leu	Gln	Gly	Ile	Asn	455	460	465
Cys	Gly	Pro	Asp	Phe	Thr	Pro	Ser	Phe	Ala	Asn	Leu	Gly	Arg	Thr	470	475	480
Thr	Leu	Ser	Thr	Arg	Gly	Pro	Pro	Arg	Gly	Gly	Pro	Gly	Gly	Glu	485	490	495
Leu	Pro	Arg	Gly	Pro	Gln	Ala	Gly	Leu	Gly	Pro	Arg	Arg	Ser	Gln	500	505	510
Gln	Gly	Pro	Arg	Lys	Glu	Pro	Arg	Lys	Ile	Ile	Ala	Thr	Val	Leu	515	520	525
Met	Thr	Glu	Asp	Ile	Lys	Leu	Asn	Lys	Ala	Glu	Lys	Ala	Trp	Lys	530	535	540
Pro	Ser	Ser	Lys	Arg	Thr	Ala	Ala	Asp	Lys	Asp	Arg	Gly	Glu	Glu	545	550	555
Asp	Ala	Asp	Gly	Ser	Lys	Thr	Gln	Asp	Leu	Phe	Arg	Arg	Val	Arg	560	565	570
Ser	Ile	Leu	Asn	Lys	Leu	Thr	Pro	Gln	Met	Phe	Gln	Gln	Leu	Met	575	580	585
Lys	Gln	Val	Thr	Gln	Leu	Ala	Ile	Asp	Thr	Glu	Glu	Arg	Leu	Lys	590	595	600
Gly	Val	Ile	Asp	Leu	Ile	Phe	Glu	Lys	Ala	Ile	Ser	Glu	Pro	Asn	605	610	615
Phe	Ser	Val	Ala	Tyr	Ala	Asn	Met	Cys	Arg	Cys	Leu	Met	Ala	Leu	620	625	630
Lys	Val	Pro	Thr	Thr	Glu	Lys	Pro	Thr	Val	Thr	Val	Asn	Phe	Arg	635	640	645
Lys	Leu	Leu	Leu	Asn	Arg	Cys	Gln	Lys	Glu	Phe	Glu	Lys	Asp	Lys			

Asp Asp Asp Glu	650	655	660
Val Phe Glu Lys Lys	665	670	675
Ala Ala Thr Ala	680	685	690
Glu Ala Arg Asp	695	700	705
Phe Ile Gly Glu	710	715	720
Met His Asp Cys	725	730	735
Ser Leu Glu Cys	740	745	750
Leu Asp Phe Glu	755	760	765
Gln Met Glu Lys	770	775	780
Arg Phe Met Leu	785	790	795
Val Pro Arg Arg	800	805	810
His Lys Glu Ala	815	820	825
Gln Gln Leu Met	830	835	840
Pro Gly Pro Pro	845	850	855
Gly Trp Asn Thr	860	865	870
Thr Ser Arg Leu	875	880	885
Asn Asn Gln Leu	890	895	900
Gly Ser Ser Gly	905	910	915
Glu Ala Ala Arg	920	925	930
Leu Gln Gln Ala	935	940	945
Val Gln Arg Ser	950	955	960
Asp Arg Gly Asp	965	970	975
Gly Asp Arg Leu	980	985	990
Phe Ser Lys Glu	995	1000	1005
Pro Glu Gly Leu	1010	1015	1020
Arg Gly Arg Asp	1025	1030	1035
Ser Pro Leu Lys	1040	1045	1050
Ser Lys Ala Ile	1055	1060	1065
Glu Ala Val Gln	1070	1075	1080

Phe	Ile	Phe	Val	Arg	His	Gly	Val	Glu	Ser	Thr	Leu	Glu	Arg	Ser	1085	1090	1095
Ala	Ile	Ala	Arg	Glu	His	Met	Gly	Gln	Leu	Leu	His	Gln	Leu	Leu	1100	1105	1110
Cys	Ala	Gly	His	Leu	Ser	Thr	Ala	Gln	Tyr	Tyr	Gln	Gly	Leu	Tyr	1115	1120	1125
Glu	Ile	Leu	Glu	Leu	Ala	Glu	Asp	Met	Glu	Ile	Asp	Ile	Pro	His	1130	1135	1144
Val	Trp	Leu	Tyr	Leu	Ala	Glu	Leu	Val	Thr	Pro	Ile	Leu	Gln	Glu	1145	1150	1155
Gly	Gly	Val	Pro	Met	Gly	Glu	Leu	Phe	Arg	Glu	Ile	Thr	Lys	Pro	1160	1165	1170
Leu	Arg	Pro	Leu	Gly	Lys	Ala	Ala	Ser	Leu	Leu	Leu	Glu	Ile	Leu	1175	1180	1185
Gly	Leu	Leu	Cys	Lys	Ser	Met	Gly	Pro	Lys	Lys	Val	Gly	Thr	Leu	1190	1195	1200
Trp	Arg	Glu	Ala	Gly	Leu	Ser	Trp	Lys	Glu	Phe	Leu	Pro	Glu	Gly	1205	1210	1215
Gln	Asp	Ile	Gly	Ala	Phe	Val	Ala	Glu	Gln	Lys	Val	Glu	Tyr	Thr	1220	1225	1230
Leu	Gly	Glu	Glu	Ser	Glu	Ala	Pro	Gly	Gln	Arg	Ala	Leu	Pro	Ser	1235	1240	1245
Glu	Glu	Leu	Asn	Arg	Gln	Leu	Glu	Lys	Leu	Leu	Lys	Glu	Gly	Ser	1250	1255	1260
Ser	Asn	Gln	Arg	Val	Phe	Asp	Trp	Ile	Glu	Ala	Asn	Leu	Ser	Glu	1265	1270	1275
Gln	Gln	Ile	Val	Ser	Asn	Thr	Leu	Val	Arg	Ala	Leu	Met	Thr	Ala	1280	1285	1290
Val	Cys	Tyr	Ser	Ala	Ile	Ile	Phe	Glu	Thr	Pro	Leu	Arg	Val	Asp	1295	1300	1305
Val	Ala	Val	Leu	Lys	Ala	Arg	Ala	Lys	Leu	Leu	Gln	Lys	Tyr	Leu	1310	1315	1320
Cys	Asp	Glu	Gln	Lys	Glu	Leu	Gln	Ala	Leu	Tyr	Ala	Leu	Gln	Ala	1325	1330	1335
Leu	Val	Val	Thr	Leu	Glu	Gln	Pro	Pro	Asn	Leu	Leu	Arg	Met	Phe	1340	1345	1350
Phe	Asp	Ala	Leu	Tyr	Asp	Glu	Asp	Val	Val	Lys	Glu	Asp	Ala	Phe	1355	1360	1365
Tyr	Ser	Trp	Glu	Ser	Ser	Lys	Asp	Pro	Ala	Glu	Gln	Gln	Gly	Lys	1370	1375	1380
Gly	Val	Ala	Leu	Lys	Ser	Val	Thr	Ala	Phe	Phe	Lys	Trp	Leu	Arg	1385	1390	1395
Glu	Ala	Glu	Glu	Glu	Ser	Asp	His	Asn							1400		

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<210> 37
<211> 322
<212> PRT
<213> Homo sapiens
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<300>
<308> Incyte ID No.: g2440051

<400> 37

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Lys Leu Ile Ser Val Pro Asp Ile Leu Pro Lys Glu Val Ile Glu
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Ser Cys Gly Met Arg Thr Glu Gly Glu Arg Thr Gln Val Tyr Lys
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Gly Leu Gln Glu Glu Lys Gly Ile Tyr Arg Val His Gln Phe Asn
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Lys Val Glu Met Phe Ala Ile Cys Thr Glu Glu Gln Ser Glu Ala
          170          175          180
Glu Leu Glu Glu Phe Lys Asn Ile Glu Val Asp Leu Phe Arg Arg
          185          190          195
Leu Gly Leu Asn Phe Arg Leu Leu Asp Met Pro Pro Cys Glu Leu
          200          205          210
Gly Ala Pro Ala Tyr Gln Lys Tyr Asp Ile Glu Ala Trp Met Pro
          215          220          225
Gly Arg Gln Met Trp Gly Glu Ile Ser Ser Cys Ser Asn Cys Thr
          230          235          240
Asp Tyr Gln Ala Arg Arg Leu Gly Ile Arg Tyr Arg Arg Ser Ala
          245          250          255
Asp Gly Gln Ile Leu His Ala His Thr Ile Asn Gly Thr Ala Thr
          260          265          270
Ala Ile Pro Arg Leu Leu Ile Ala Leu Leu Glu Ser Tyr Gln Lys
          275          280          285
Glu Asp Gly Ile Glu Ile Pro Ala Val Leu Arg Pro Phe Met Asp
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<212> PRT

<213> Homo sapiens

<300>

<308> Incyte ID No.: g1808648

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 20      25      30
His Phe Gly Ile His Glu Glu Met Leu Lys Asp Glu Val Arg Thr
 35      40      45
Leu Thr Tyr Arg Asn Ser Met Phe His Asn Arg His Leu Phe Lys
 50      55      60
Asp Lys Val Val Leu Asp Val Gly Ser Gly Thr Gly Ile Leu Cys
 65      70      75
Met Phe Ala Ala Lys Ala Gly Ala Arg Lys Val Ile Gly Ile Val
 80      85      90
Cys Ser Ser Ile Ser Asp Tyr Ala Val Lys Ile Val Lys Ala Asn
 95      100     105
Lys Leu Asp His Val Val Thr Ile Ile Lys Gly Lys Val Glu Glu
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Val Glu Leu Pro Val Glu Lys Val Asp Ile Ile Ile Ser Glu Trp
 125     130     135
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Lys Asp Tyr Lys Ile His Trp Trp Glu Asn Val Tyr Gly Phe Asp
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Met Ser Cys Ile Lys Asp Val Ala Ile Lys Glu Pro Leu Val Asp
 200     205     210
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 215     220     225
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 230     235     240
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 245     250     255
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 260     265     270
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 320     325     330
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, 5/10, 1/21, C07K 14/47, 16/18, A61K 38/17, C12Q 1/68		A3	(11) International Publication Number: WO 00/15799 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/US99/21688 (22) International Filing Date: 17 September 1999 (17.09.99) (30) Priority Data: 60/155,246 17 September 1998 (17.09.98) US 09/158,720 22 September 1998 (22.09.98) US Not furnished 22 September 1998 (22.09.98) US 60/069,391 4 November 1998 (04.11.98) US 60/128,660 8 April 1999 (08.04.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US Not furnished (CIP) Filed on 17 September 1998 (17.09.98) US 09/158,720 (CIP) Filed on 22 September 1998 (22.09.98) US Not furnished (CIP) Filed on 22 September 1998 (22.09.98) US 09/186,815 (CIP) Filed on 4 November 1998 (04.11.98) US 09/156,039 (CIP) Filed on 17 September 1998 (17.09.98) US Not furnished (CIP) Filed on 4 November 1998 (04.11.98) US 60/128,660 (CIP)			Filed on 8 April 1999 (08.04.99) (71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). GORGONE, Gina, A. [US/US]; 1253 Pincrest Drive, Boulder Creek, CA 95006 (US). PATTERSON, Chandra [US/US]; 490 Sherwood Way #1, Menlo Park, CA 94025 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). YANG, Junming [CN/US]; 7136 Clarendon Street, San Jose, CA 95129 (US). (74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 13 July 2000 (13.07.00)

(54) Title: RNA-ASSOCIATED PROTEINS**(57) Abstract**

The invention provides human RNA-associated proteins (RNAAP) and polynucleotides which identify and encode RNAAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonist. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of RNAAP.

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INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 99/21688

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N5/10 C12N1/21 C07K14/47 C07K16/18
A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMHUM1 [Online] E.M.B.L. Databases Accession Number: AF047448, 17 March 1998 (1998-03-17) YANG L ET AL: "Homo sapiens TLS-associated protein TASR mRNA, complete cds" XP002128498 99.5% identity in 621 bp overlap with SeqIdNo.26 / 100% identity in 155 aa overlap with SeqIdNo.1 abstract	1-16,19
P,X	-& YANG L ET AL: "Oncoprotein TLS interacts with serine-arginine proteins involved in RNA splicing" JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 273, no. 43, 23 October 1998 (1998-10-23), pages 27761-27764, XP002128497 the whole document -/-	1-16,19

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 January 2000

Date of mailing of the international search report

02.05.2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Lonnoy, O

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 99/21688

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	--- EP 0 679 716 A (MATSUBARA KENICHI ;OKUBO KOUSAKU (JP)) 2 November 1995 (1995-11-02) Human gene signature HUMGS00127 (SeqIdNo.113): 98.9% identity in 349 bp overlap with SeqIdNo.26	3-11
X	-& DATABASE GENESEQ [Online] E.M.B.L. Databases Accession Number: T19113, 4 July 1996 (1996-07-04) MATSUBARA K ET AL: "Human gene signature HUMGS00127" XP002128499 98.9% identity in 349 bp overlap with SeqIdNo.26 abstract	3-11
A	--- US 5 561 222 A (KEENE JACK D ET AL) 1 October 1996 (1996-10-01) figure 6	
A	--- WO 98 23744 A (INCYTE PHARMA INC ;BANDMAN OLGA (US); GOLI SURYA K (US)) 4 June 1998 (1998-06-04) -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 21688

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheet, subject 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-20 (all partially)

A substantially purified polypeptide of SeqIdNo.1, a fragment of said polypeptide; an isolated and purified polynucleotide encoding said polypeptide, a variant polynucleotide having at least 90% sequence identity to said polynucleotide, a polynucleotide hybridising to said polynucleotide, a polynucleotide having a sequence complementary to said polynucleotide; a detection method using said complementary polynucleotide; a polynucleotide comprising a sequence of SeqIdNo.18 or a fragment thereof, a polynucleotide having at least 90% sequence identity to said polynucleotide of SeqIdNo.18, a polynucleotide complementary to said polynucleotide of SeqIdNo.18; expression vector, host and recombinant method related thereto; a pharmaceutical composition comprising said polypeptide of SeqIdNo.1; an antibody to said polypeptide of SeqIdNo.1 or fragment of said polypeptide of SeqIdNo.1; an agonist to said polypeptide of SeqIdNo.1; an antagonist to said polypeptide of SeqIdNo.1; therapeutic application thereof

Inventions 2-17: claims 1-20 (all partially)

Idem as for subject 1 but limited to each of the polypeptide sequences as in SeqIdNo.2-17 and the corresponding polynucleotide sequences as in SeqIdNo.19-34, wherein respectively invention 2 is limited to SeqIdNo.2 and SeqIdNo.19, invention 3 is limited to SeqIdNo.3 and SeqIdNo.20,..., invention 17 is limited to SeqIdNo.17 and SeqIdNo.34.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Claims Nos.: 17,18,20

Claims 17, 18 and 20 refer to an agonist, an antagonist and to the use of an antagonist of the polypeptide of claim 1 without giving a true technical characterization. Moreover, no such compound is defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such speculative claims the wording of which is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/21688

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0679716	A	02-11-1995	AU 8116494 A	13-06-1995
			CA 2153480 A	01-06-1995
			WO 9514772 A	01-06-1995

US 5561222	A	01-10-1996	US 5866680 A	02-02-1999

WO 9823744	A	04-06-1998	US 5962226 A	05-10-1999
			AU 7410598 A	22-06-1998

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209 CTNLTLE V

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